Health Canada Santé Canada
Your health and safety… our priority. Votre santé et votre sécurité… notre priorité.

Proposed Registration Decision PRD2016-03

# Mandestrobin

(publié aussi en français)

**29 January 2016**

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6607 D
Ottawa, Ontario K1A 0K9

Internet: pmra.publications@hc-sc.gc.ca
healthcanada.gc.ca/pmra
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra.infoserv@hc-sc.gc.ca

Canada

ISSN: 1925-0878 (print)
1925-0886 (online)

Catalogue number: H113-9/2016-03E (print version)
H113-9/2016-03E-PDF (PDF version)

**© Her Majesty the Queen in Right of Canada, represented by the Minister of Health Canada, 2016**

All rights reserved. No part of this information (publication or product) may be reproduced or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, or stored in a retrieval system, without prior written permission of the Minister of Public Works and Government Services Canada, Ottawa, Ontario K1A 0S5.

# Table of Contents

Overview .......... 1
  Proposed Registration Decision for Mandestrobin .......... 1
  What Does Health Canada Consider When Making a Registration Decision? .......... 1
  What Is Mandestrobin? .......... 2
  Health Considerations .......... 2
  Environmental Considerations .......... 4
  Value Considerations .......... 5
  Measures to Minimize Risk .......... 5
  Next Steps .......... 6
  Other Information .......... 6
Science Evaluation .......... 7
  1.0 The Active Ingredient, Its Properties and Uses .......... 7
    1.1 Identity of the Active Ingredient .......... 7
    1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Products .......... 8
    1.3 Directions for Use .......... 9
    1.4 Mode of Action .......... 10
  2.0 Methods of Analysis .......... 10
    2.1 Methods for Analysis of the Active Ingredient .......... 10
    2.2 Method for Formulation Analysis .......... 10
    2.3 Methods for Residue Analysis .......... 10
  3.0 Impact on Human and Animal Health .......... 10
    3.1 Toxicology Summary .......... 10
      3.1.1 *Pest Control Products Act* Hazard Characterization .......... 14
    3.2 Acute Reference Dose (ARfD) .......... 15
    3.3 Acceptable Daily Intake .......... 15
    3.4 Occupational and Residential Risk Assessment .......... 16
      3.4.1 Toxicological Endpoints .......... 16
      3.4.2 Occupational Exposure and Risk .......... 17
      3.4.3 Residential Exposure and Risk Assessment .......... 23
    3.5 Food Residues Exposure Assessment .......... 25
      3.5.1 Residues in Plant and Animal Foodstuffs .......... 25
      3.5.2 Concentrations in Drinking Water .......... 26
      3.5.3 Dietary Risk Assessment .......... 27
      3.5.4 Aggregate Exposure and Risk .......... 28
      3.5.5 Maximum Residue Limits .......... 28
  4.0 Impact on the Environment .......... 29
    4.1 Fate and Behaviour in the Environment .......... 29
    4.2 Environmental Risk Characterization .......... 30
      4.2.1 Risks to Terrestrial Organisms .......... 30
      4.2.2 Risks to Aquatic Organisms .......... 32
      4.2.3 Further characterization of risk to aquatic organisms .......... 34

5.0 Value ... 35
5.1 Consideration of Benefits ... 35
5.2 Effectiveness Against Pests ... 35
5.3 Non-Safety Adverse Effects ... 36
5.4 Supported Uses ... 36
6.0 Pest Control Product Policy Considerations ... 36
6.1 Toxic Substances Management Policy Considerations ... 36
6.2 Formulants and Contaminants of Health or Environmental Concern ... 37
7.0 Summary ... 37
7.1 Human Health and Safety ... 37
7.2 Environmental Risk ... 38
7.3 Value ... 39
8.0 Proposed Regulatory Decision ... 39
List of Abbreviations ... 41
Appendix I Tables and Figures ... 47
Table 1a Residue Analysis for Environmental Media ... 47
Table 1b Residue Analysis for Crops ... 47
Table 2 Chemical Names of Isomers and Metabolites of Mandestrobin ... 48
Table 3 Toxicity Profile of S-2200 3.2 FS Fungicide ... 48
Table 4 Toxicity Profile of S-2200 4 SC Fungicide, S-2200 4 SC AG Fungicide and S-2200 4 SC VPP Fungicide ... 49
Table 5 Toxicity Profile of Technical Mandestrobin ... 50
Table 6 Toxicity Profile of Metabolites of Mandestrobin ... 54
Table 7 Toxicology Endpoints for Use in Health Risk Assessment for Mandestrobin. 55
Table 8 Integrated Food Residue Chemistry Summary ... 56
Table 9 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment ... 69
Table 10 Fate and Behaviour in the Environment ... 70
Table 11 Major Transformation Products Formed in the Environment ... 77
Table 12 Toxicity of Mandestrobin and Transformation Products to Non-Target Terrestrial Species ... 79
Table 13 Screening Level and Refined Risk Assessment of Mandestrobin for Non-Target Species, Other than Birds and Mammals ... 80
Table 14 Screening Level Risk Assessment of Foliar Application of Mandestrobin for Birds and Mammals ... 81
Table 15 Screening Level Assessment of Seed Treatment with Mandestrobin for Birds and Mammals ... 82
Table 16 Toxicity of Mandestrobin, S-2200-*R*-Isomer, S-2200-*S*-Isomer and Transformation Products to Non-Target Aquatic Species ... 82
Table 17 Screening Level Risk Assessment of Mandestrobin to Aquatic Organisms ... 85
Table 18 Screening Level Risk Assessment of Mandestrobin Isomers and Transformation Products for Terrestrial and Aquatic Organisms ... 85
Table 19 Refined Risk Assessment of Potential Risk from Drift of Mandestrobin, S-2200 R-isomer and the Transformation Product S-2200-ORC to Aquatic Organisms ... 86

Table 20 Risk Quotients for Aquatic Organisms Determined for Runoff of Mandestrobin, S-2200-*R*-Isomer and S-2200-ORC in Water Bodies .............. 87
Table 21 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria .............. 87
Table 22 Fungicide Resistance Action Committee modes of action groups of currently registered alternative products (as of June 2015) .............. 88
Table 23 List of Supported Uses .............. 89
Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications .............. 91
Table 1 Comparison of Canadian MRLs, American Tolerances and Codex MRLs .............. 91
References .............. 93

# Overview

## Proposed Registration Decision for Mandestrobin

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Mandestrobin Technical (previously known as S-2200 Fungicide Technical) and the associated end-use products: S-2200 4 SC Fungicide, Intuity Fungicide (previously known as S-2200 4 SC Ag Fungicide), Pinpoint Fungicide (previously known as S-2200 4 SC VPP Fungicide), and S-2200 3.2 FS Fungicide, containing the technical grade active ingredient mandestrobin, for the management of various fungal diseases in canola and other oilseed crops, corn, grape, legume vegetables, strawberry and other low growing berries, as well as turfgrass.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of S-2200 Fungicide Technical, S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, S-2200 4 SC VPP Fungicide, and S-2200 3.2 FS Fungicide.

## What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

---

[1] "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

[2] "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "… the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

Before making a final registration decision on mandestrobin, the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on mandestrobin, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

## What Is Mandestrobin?

Mandestrobin is the active ingredient in the following fungicide products that are being proposed for registration in Canada: S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, S-2200 4 SC VPP Fungicide, and S-2200 3.2 FS Fungicide. These products are formulated for either foliar or seed applications and are intended for the management of various fungal diseases in canola and other oilseed crops, corn, grape, legume vegetables, strawberry and other low growing berries, as well as turfgrass. Mandestrobin has preventative and systemic properties and acts by interfering with the cellular mechanisms in susceptible fungal pathogens.

## Health Considerations

### Can Approved Uses of Mandestrobin Affect Human Health?

**Products containing mandestrobin are unlikely to affect your health when used according to label directions.**

Potential exposure to mandestrobin may occur through the diet (food and water) or when handling and applying the products. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

---

[3] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

[4] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, the technical grade active ingredient mandestrobin was of low acute toxicity by the oral, dermal and inhalation routes. Mandestrobin was minimally irritating to the eye and non-irritating to the skin. Mandestrobin did not cause allergic skin reactions.

The acute toxicity of the end-use products was low via the oral, dermal and inhalation routes of exposure. The products were non-irritating to the skin and minimally irritating to the eyes. They did not cause allergic skin reactions. Consequently, no hazard signal words are required on their labels.

Applicant-supplied short- and long-term (lifetime) animal toxicity tests were assessed for the potential of mandestrobin to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment were adverse effects noted on growth and in the liver, bile duct, and kidneys. There was a low level of concern for sensitivity of the young animal. The risk assessment protects against the finding noted above as well as any other potential effects by ensuring that the level of exposure to humans is well below the lowest dose at which these effects occurred in animal tests.

### Residues in Water and Food

**Dietary risks from food and drinking water are not of health concern.**

Aggregate dietary intake estimates (food plus drinking water) revealed that the general population and children 1-2 years old, the subpopulation which would ingest the most mandestrobin relative to body weight, are expected to be exposed to less than 10% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from mandestrobin is not of health concern for all population subgroups.

Animal studies revealed no acute health effects. Consequently, a single dose of mandestrobin is not likely to cause acute health effects in the general population (including infants and children). Mandestrobin is not carcinogenic; therefore, a cancer dietary risk assessment is not required.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada (and the United States) using mandestrobin on rapeseed, corn, grapes, strawberries, and soybeans are acceptable. The MRLs for this active ingredient can be found in the Science Evaluation of this consultation document.

### Occupational Risks From Handling S-2200 4 SC Fungicide, S-2200 3.2 FS Fungicide, S-2200 4 SC Ag Fungicide, and S-2200 4 SC VPP Fungicide

**Occupational risks are not of concern when S-2200 4 SC Fungicide, S-2200 3.2 FS Fungicide, S-2200 4 SC Ag Fungicide and S-2200 4 SC VPP Fungicide are used according to the label directions, which include protective measures.**

Farmers, custom applicators, seed treaters and planters who mix, load, apply or treat seeds with S-2200 4 SC Fungicide, S-2200 3.2 FS Fungicide, S-2200 4 SC Ag Fungicide, and S-2200 4 SC VPP Fungicide, as well as field workers re-entering freshly treated fields, can come in direct contact with residues on the skin. Therefore, the label specifies that anyone mixing/loading and applying S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, and S-2200 4 SC VPP Fungicide must wear a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks. The field crew and the mixer/loaders for aerial applications of S-2200 4 SC Ag Fungicide must wear coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks, and goggles or face shield during mixing/loading, cleanup and repair. The label also requires that workers do not enter treated fields for 12 hours after application. Workers treating seeds with S-2200 3.2 FS Fungicide must use closed transfer systems in commercial facilities (excluding mobile treaters), and must wear long pants, a long-sleeved shirt and chemical-resistant gloves, shoes and socks during mixing, loading, treating, bagging, sewing or stacking of bagged treated seed, handling treated seed, and planting treated seed. In addition, seed treatment workers performing cleaning, maintenance, and repair of seed treatment equipment must wear chemical-resistant coveralls. As well, standard label statements to protect against drift during application are on the labels. Taking into consideration these label statements, the use pattern, and the duration of exposure for handlers and workers, risks to these individuals are not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

## Environmental Considerations

### What Happens When Mandestrobin Is Introduced Into the Environment?

**When used according to label directions mandestrobin is not expected to pose an unacceptable risk to the environment.**

Mandestrobin enters the environment when applied as a foliar spray, seed treatment or chemigation. Mandestrobin can break down in the presence of microbes in terrestrial systems. Laboratory studies indicate mandestrobin has the potential to be persistent in certain soils, whereas field studies indicate that mandestrobin is less likely to persist in the environment. The properties of mandestrobin and its transformation products, 5-COOH-S-2200 and 2-COOH-S-2200, indicate some potential for downward movement through the soil. However, field studies and modelling indicate that levels of mandestrobin and its transformation products that may reach groundwater are low. In aquatic systems, mandestrobin will move out of the water column and into sediments where it has the potential to persist.

Mandestrobin does not break down by reacting with water, but it can break down rapidly in the presence of sunlight, especially in clear shallow waters. It is not expected to accumulate in the tissues of aquatic organisms. Mandestrobin is not expected to enter the atmosphere nor be transported long distances from where it was applied.

When used according to label directions, mandestrobin is expected to pose a negligible risk to earthworms, bees, beneficial arthropods, birds and small mammals. If exposed to high enough concentrations, mandestrobin may pose a risk to non-target aquatic organisms and terrestrial plants. Risks to non-target aquatic organisms and terrestrial plants can be mitigated with label statements and spray buffer zones to protect sensitive aquatic and terrestrial habitats. Label statements are required on the product labels to inform the users of the potential risks.

## Value Considerations

### What Is the Value of S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, S-2200 4 SC VPP Fungicide, and S-2200 3.2 FS Fungicide?

**These products have demonstrated good efficacy and will provide growers with additional product options for the management of a broad range of common diseases in economically important crops in Canada.**

S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, and S-2200 4 SC VPP Fungicide are formulated for foliar spray applications to control or suppress a range of diseases on oil seed crops, grape, low growing berries including strawberry, and turfgrass. S-2200 3.2 FS Fungicide is applied as a seed treatment to control various common fungi that cause seed rots in corn, legume vegetables, and oil seed crops. Mandestrobin is most effective when applied preventatively or at the early stages of disease development. Appropriate use of these products will help growers maximize the quality and yield of their crops.

## Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of S-2200 4 SC Fungicide, S-2200 3.2 FS Fungicide, S-2200 4 SC Ag Fungicide, and S-2200 4 SC VPP Fungicide to address the potential risks identified in this assessment are as follows.

### Key Risk-Reduction Measures

### Human Health

Because there is a concern with users coming into direct contact with S-2200 4 SC Fungicide, S-2200 3.2 FS Fungicide, S-2200 4 SC Ag Fungicide, and S-2200 4 SC VPP Fungicide on the skin or through inhalation of spray mists, anyone mixing, loading and applying S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, and S-2200 4 SC VPP Fungicide must wear a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks. The field crew and the mixer/loaders for aerial applications of S-2200 4 SC Ag Fungicide must wear coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks, and goggles or face shield during mixing/loading, cleanup and repair. The label also requires that workers do not enter treated fields for 12 hours after application.

Workers treating seeds with S-2200 3.2 FS Fungicide must use closed transfer systems in commercial facilities (excluding mobile treaters), and must wear long pants, a long-sleeved shirt and chemical-resistant gloves, shoes and socks during mixing, loading, treating, bagging, sewing or stacking of bagged treated seed, handling treated seed, and planting treated seed. In addition, seed treatment workers performing cleaning, maintenance, and repair of seed treatment equipment must wear chemical-resistant coveralls. Standard label statements to protect against drift during application are also on the labels.

### Environment

Mandestrobin can pose a risk to non-target aquatic organisms and terrestrial plants. To mitigate potential exposures to mandestrobin via spray drift, spray buffer zones of 0 to 15 metres are required to protect sensitive terrestrial and aquatic habitats, depending on the method of application. These spray buffer zones are to be specified on the product labels.

## Next Steps

Before making a final registration decision on mandestrobin, the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

## Other Information

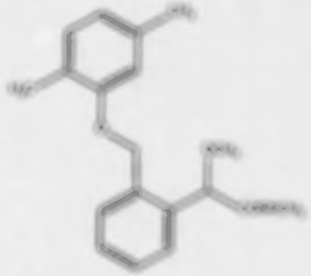
When the PMRA makes its registration decision, it will publish a Registration Decision on mandestrobin (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

# Science Evaluation

**Mandestrobin**

## 1.0 The Active Ingredient, Its Properties and Uses

### 1.1 Identity of the Active Ingredient

| | |
|---|---|
| **Active substance** | Mandestrobin |
| **Function** | Fungicide |
| **Chemical name** | |
| **1. International Union of Pure and Applied Chemistry (IUPAC)** | *rac*-(2*R*)-2-{2-[(2,5-dimethylphenoxy)methyl]phenyl}-2-methoxy-*N*-methylacetamide |
| **2. Chemical Abstracts Service (CAS)** | 2-[(2,5-dimethylphenoxy)methyl]-α-methoxy-*N*-methylbenzeneacetamide |
| **CAS number** | 173662-97-0 |
| **Molecular formula** | $C_{19}H_{23}NO_3$ |
| **Molecular weight** | 313.4 |
| **Structural formula** |  |
| **Purity of the active ingredient** | 98.8% |

## 1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Products

### Technical Product—S-2200 Fungicide Technical

| Property | Result |
|---|---|
| Colour and physical state | White solid |
| Odour | Odourless |
| Melting point | 102°C |
| Boiling point | 296°C |
| Relative density | 1.2017 |
| Vapour pressure at 20°C | $3.36 \times 10^{-8}$ Pa (extrapolated) |
| Ultraviolet (UV)-visible spectrum | Solution / λmax (nm) / Molar absorptivity, (ε) (mol/L)$^{-1}$cm$^{-1}$<br>Methanol / 275 / 2100<br>Acidic / 275 / 1920<br>Basic / 275 / 1880<br>Neutral / 275 / 1790 |
| Solubility in water at 20°C | 15.8 mg/L |
| Solubility in organic solvents at 20°C | Solvent / Solubility (g/L)<br>Dichloromethane / 597<br>Acetone / 552<br>Ethyl acetate / 276<br>Methanol / 182<br>Toluene / 107<br>n-Octanol / 42.6<br>Hexane / 2.00 |
| n-Octanol-water partition coefficient ($K_{ow}$) | Log $K_{ow}$ = 3.51 at 25°C |
| Dissociation constant ($pK_a$) | No dissociative activity in the pH range 2-10 |
| Stability (temperature, metal) | Stable for 14 days when exposed to normal and elevated (54°C) temperatures and metals and metal ions (iron, nickel, iron (II) acetate and nickel (II) acetate) |

### End-Use Product—S-2200 3.3 SC Fungicide

| Property | Result |
|---|---|
| Colour | White, opaque |
| Odour | Faint, paint-like odour |
| Physical state | Liquid |
| Formulation type | Suspension |
| Guarantee | 393 g/L |

| Property | Result |
|---|---|
| Container material and description | High-density polyethylene (HDPE) |
| Density at 20°C | 1.091 g/mL |
| pH of 1% dispersion in water | 5.7 at 25°C |
| Oxidizing or reducing action | No oxidizing or reducing action |
| Storage stability | In progress |
| Corrosion characteristics | In progress |
| Explodability | Not explosive |

**End-Use Product—S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide and S-2200 4 SC VPP Fungicide**

| Property | Result |
|---|---|
| Colour | White, opaque |
| Odour | Sweet odour |
| Physical state | Liquid |
| Formulation type | Suspension |
| Guarantee | 43.4% |
| Container material and description | High-density polyethylene (HDPE) |
| Density at 20°C | 1.095 g/mL |
| pH of 1% dispersion in water | 6.8 at 25°C |
| Oxidizing or reducing action | No oxidizing or reducing action |
| Storage stability | In progress |
| Corrosion characteristics | In progress |
| Explodability | Not explosive |

### 1.3 Directions for Use

S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, and S-2200 4 SC VPP Fungicide are to be applied by foliar application to labelled crops on a preventative basis or at the earliest signs of infection. The application rates range from 439 to 986 mL/ha. When repeated treatments are required and permitted, reapplication intervals range from seven to 28 days.

S-2200 3.2 FS Fungicide is applied once, directly to seed before planting. Application rates per 100 kg of seed range from 15.6 to 26 mL depending on the treated crop. Because S-2200 3.2 FS Fungicide does not contain a colourant, the product must be applied in combination with an appropriate colourant.

### 1.4 Mode of Action

Mandestrobin belongs to the quinone outside inhibitors class of fungicides. These fungicides provide control of target pathogens by interfering with their ability to produce energy, which in turn inhibits development of spores and mycelia. Mandestrobin is a broad spectrum fungicide with preventive and systemic properties. It is most effective when applied prior to infection.

## 2.0 Methods of Analysis

### 2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable for the determinations.

### 2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulations has been validated and assessed to be acceptable for use as an enforcement analytical method.

### 2.3 Methods for Residue Analysis

For environmental media, high-performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis of environmental media are summarized in Appendix I, Table 1a.

For crops, high performance liquid chromatography methods with tandem mass spectrometric detection (HPLC-MS/MS; Method RM-48C-2A) in plant matrices was developed and proposed for data gathering and enforcement purposes for the determination of mandestrobin residues. The method fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation (0.02 ppm). Acceptable recoveries (70–120%) were obtained in plant matrices. The proposed enforcement method was successfully validated in plant matrices by an independent laboratory. In addition the extraction solvents used in the method were similar to those used in the metabolism studies. Method RM-48M-1 was developed and proposed for enforcement purposes for poultry muscle only. Methods for residue analysis of crops are summarized in Appendix I, Table 1b.

## 3.0 Impact on Human and Animal Health

### 3.1 Toxicology Summary

A detailed review of the toxicological database for mandestrobin was conducted. The database is complete, consisting of the full array of toxicity studies required for hazard assessment purposes. The studies were carried out in accordance with accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to mandestrobin. Mechanistic studies were also provided to support a proposed mode of action (MOA) for the thyroid effects in rats, and to investigate a possible effect of mandestrobin and its major metabolites on human estrogen and androgen receptors, as well as a possible effect of mandestrobin on the steroidogenesis of testosterone and estrogen. Acute oral toxicity and mutagenicity assays were also provided for five of the metabolites of mandestrobin observed in the rat.

Mandestrobin (S-2200TG, RS-Mandestrobin) is a racemic mixture of isomers R-mandestrobin (S-2167) and S-mandestrobin (S-2354). The metabolism and pharmacokinetics of mandestrobin were characterised after single oral gavage administration (racemic mixture at low and high doses and separate isomers at a low dose) and multiple oral gavage administration (14-day treatment at a low dose). All forms of mandestrobin, radiolabelled on either benzyl (mandestrobin, R-isomer and S-isomer) or phenoxy (mandestrobin) ring, were rapidly absorbed after a single gavage dose in rats. Area under the curve was proportionally higher at the low dose than at the high dose, indicating saturation of oral absorption at the high dose. Peak plasma levels were reached by 1.2 to 2.6 hours after an oral low dose, and 7.0 to 9.1 hours after a high dose. The labeled compound was widely distributed throughout tissues, but was detected primarily in the gastrointestinal (GI) tract, liver and kidney. Pancreas, uterus and ovaries also had higher levels than most other tissues. Mandestrobin isomers had similar tissue distribution, except the S-isomer was more prevalent in the GI tract than the R-isomer. There were no sex differences in tissue distribution, with the exception of the repeat-dose study in which females retained a larger portion of the dose in the cecum/large intestine/intestinal contents, and reached peak levels in tissues outside the GI tract later than males.

There was no evidence of accumulation of mandestrobin or its metabolites in tissues following repeated dosing. Clearance of a single dose of mandestrobin from plasma was almost complete by 120 hours post-dose. Clearance of the S-isomer was less rapid than the R-isomer. In the repeated-dose study, the majority of the administered dose was excreted by 14 days after last dose. Bile-cannulated rats excreted the radiolabelled compound more quickly than non-cannulated rats, suggesting enterohepatic recirculation. Excretion was consistent with all mandestrobin treatments. Fecal excretion via bile was the primary route, and renal excretion was also important. Excretion in expired air was negligible.

Mandestrobin was almost completely metabolized in rats via (1) oxidation followed by glucuronidation, or (2) demethylation followed by oxidation, or (3) oxidation followed by demethylation. There was no cleavage of benzyl and phenoxy rings. The major metabolites excreted were: 5-CA-S-2200-NHM and 4-OH-S-2200 in feces; 4-OH-S-2200-Glucuronide A in bile; and 5-CA-S-2200-NHM in urine. The same metabolites were identified for both isomers however at different proportions. Treatment with the R-isomer resulted in the following fecal/urinary metabolites in decreasing order of magnitude: 5-CA-S-2200-NHM, 5-CA-MCBX-NDM, 5-CA-2-HM-S-2200-NHM and 5-CA-S-2200-NDM; while S-isomer produced mostly 4-OH-S-2200 and 5-COOH-S-2200. In the multiple-dose study, fecal metabolites found at slightly higher levels in males than females included 5-CA-S-2200-NHM, 5-COOH-S-2200, 5-CA-2-HM-S-2200-NHM, 5-CA-2-HM-MCBX and 5-CA-MCBX-NDM. Results from cannulated rats suggest that 4-OH-S-2200 and its A glucuronide (GlucA) underwent enterohepatic circulation.

In acute toxicity testing, mandestrobin was demonstrated to be of low toxicity via the oral, dermal and inhalation routes in rats. Mandestrobin was minimally irritating to the eye and non-irritating to the skin of rabbits. Mandestrobin was not a dermal sensitizer in guinea pigs (Maximization Test).

The acute toxicity of the end-use products containing mandestrobin was low via the oral, dermal and inhalation routes in rats. The products were non-irritating to the skin and minimally irritating to the eyes of rabbits. They did not elicit a sensitization reaction in mice in the Local Lymph Node Assay.

In a short-term dermal toxicity study in rats, no adverse effects were noted at the limit dose. In repeated-dose dietary short-term studies, the liver and bile duct were the target organs of toxicity; the thyroid gland was also affected. Hepatic effects were noted in dogs and rats including hepatocellular hypertrophy accompanied by increased liver weight. At the lowest observed adverse effect level (LOAEL), increased incidences and severity of hepatocyte hypertrophy accompanied by centrilobular degeneration, liver agonal congestion and/or hemorrhage, large and dark liver, bile duct brown pigmentation and periductular inflammation, increased total cholesterol and serum liver enzymes and increased incidence and severity of thyroid follicular hypertrophy were observed. It was concluded based on the results of special mechanistic studies that, the effects on the thyroid gland were secondary to the liver effects, and were not observed without liver hypertrophy. The liver and thyroid effects were not observed in mice.

Rats and mice received a repeated dose of the test substance in the diet over most of their life span. Liver and thyroid gland effects were noted in rats at a lower dose than what was observed in short-term studies. Liver vacuolation was observed at the high dose in male rats and at the mid-high dose in female rats. Mice seemed less sensitive to the liver effects with adverse effects noted at the highest dose tested only. In long-term studies, the kidneys were a target organ of toxicity in male mice and female rats, which showed an increased incidence of corticomedullary mineralisation. According to scientific publications, the clinical significance of this observation is unclear.

However, this effect was observed in two species and different sexes in a dose-response manner, it was considered treatment-related and adverse. In female rats, renal corticomedullary mineralisation was accompanied by body weight effects, but liver and thyroid effects were only apparent at a higher dose.

MOA studies were provided to explain the liver and thyroid changes observed mostly in rats and dogs. Seven- and 14-day dietary treatments with mandestrobin caused an early induction of liver enzymes at the low dose, and, at mid-high and high dose, increased liver and thyroid gland weight and hepatocyte DNA synthesis, diffuse hepatocellular hypertrophy and diffuse thyroid follicular cell hypertrophy. In addition, effects on thyroxine, triiodothyronine, thyroid-stimulating hormone levels and T4-UDP-glucuronosyltransferase activity consistent with increased clearance of thyroxine were observed.

To evaluate reversibility of these findings, a 7-day dietary treatment followed by a 7-day recovery period was performed. The results demonstrated that most of these effects were transient and reversible. Taken together, the liver MOA studies demonstrated that the thyroid gland effects were secondary to the liver effects.

There was an increased incidence of benign ovary sex cord-stromal tumours in female rats in the long term toxicity study. Although this effect showed a dose-response relationship, it was considered as equivocal evidence of oncogenicity as this type of tumour is commonly observed in aging rats. The first tumour was observed late in the study in the control group (week 91) and later in treatment groups (week 98). No malignant tumors of this type were observed. The concern for this finding was tempered by its occurrence at a relatively high dose.

MOA studies were provided to investigate the ovary sex-cord stromal tumours observed in female rats. A reporter gene assay performed on HeLa cells derived from human uterine cervix carcinoma suggested that mandestrobin and its major metabolites (5-COOH-S-2200, 4-OH-S-2200, 5-CH2OH-S-2200 and 5-CA-S-2200-NHM) did not have agonistic or antagonistic effects on the human estrogen receptor alpha (hERa) and the human androgen receptor (hAR). Confidence in these assays was limited given that they were performed only once. The effect of mandestrobin on the production of testosterone and estradiol was evaluated in a well conducted steroidogenesis assay and the results were negative.

Although these mechanistic studies provide useful input to the mandestrobin toxicology database, they do not constitute an acceptable MOA to explain the incidence of ovary sex cord-stromal tumors in female rats.

Mandestrobin tested negative for genotoxicity in several assays, including bacterial reverse mutation assay, a forward mutation assay in mammalian cells, a chromosomal aberration assay, and an in vivo micronucleus assay.

In a two-generation dietary reproductive toxicity study in rats, there was no treatment-related effect on reproductive performance. Effects observed in parental animals were consistent with those reported in other repeated-dose dietary studies in rats and included increased liver weight and increased incidence of hypertrophy, brown pigmentation of the bile duct and periductular inflammatory cell infiltration. At a higher dose level, offspring of $F_1$ and $F_2$ generations exhibited reduced body weights beginning on postnatal day seven. In this study, there was no evidence of sensitivity of the young.

In a gavage developmental toxicity study in rats, developmental effects included increased incidences of litters with distended ureter or delayed skull ossification. These findings occurred at the limit dose of testing in the absence of maternal toxicity, thus providing evidence of sensitivity of the young. The incidences in control animals for these variations were on the low end of the historical control range. Also, clear signs of toxicity were observed at a lower dose in adult animals in other short-term studies. For these reasons the level of concern for these variations was low. No adverse effects were observed in rabbit dams exposed to mandestrobin via gavage or in their fetuses.

In an acute gavage neurotoxicity study in rats, decreased overall locomotor activity was noted in both sexes at 0-30 minutes on study day zero at the highest dose tested. This effect was considered an indicator of general toxicity rather that of specific neurotoxicity. In a 90-day dietary neurotoxicity study, decreased body weight and food consumption were noted, but no signs of neurotoxicity were noted at any time during the study. Overall, the evidence did not suggest that mandestrobin was a frank neurotoxicant.

In a 28-day dietary immunotoxicity study conducted in rats, there was an increase in spleen weight at a dose exceeding the limit dose of testing. Mandestrobin was not considered immunotoxic.

Oral acute studies and mutagenicity studies were also provided for some of the metabolites of mandestrobin. From the results of these studies, it was concluded that the metabolites 2-CH2OH-S-2200, 2-COOH-S-2200, 4-OH-S-2200, 5-COOH-S-2200 and De-Xy-S-2200 should be considered of comparable toxicity to the parent.

The code names for mandestrobin isomers and metabolites can be found in Appendix I, Table 2. Results of the toxicology studies conducted on laboratory animals with mandestrobin and its associated end-use products are summarized in Appendix I, Tables 3, 4, 5 and 6. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 7.

**Incident Reports**

Since 26 April 2007, registrants have been required by law to report incidents to the PMRA, including adverse effects to Canadian health or the environment. Mandestrobin is a new active ingredient pending registration for use in Canada. No human or domestic animal incidents involving the active ingredient mandestrobin have been reported to the PMRA and the applicant did not submit any additional data.

### 3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database contains the standard complement of required studies including gavage developmental toxicity studies in rats and rabbits and a two-generation dietary reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of fetuses or offspring compared to parental animals in the reproductive toxicity study in rats and prenatal developmental toxicity study in rabbits. Minor developmental variations (increased incidence of delayed skull ossification and distended ureters) were observed in the rat developmental toxicity study in the absence of maternal toxicity. The concern for this finding was low in view of the fact that it occurred at the limit dose of testing and toxicity was evident at this dose in other short-term studies (body weight effects, liver and thyroid effects). Furthermore, the incidences of these variations just slightly exceeded the laboratory historical data range.

Overall, the database is adequate for determining the sensitivity of the young. Concern for sensitivity was low and there were no serious endpoints were noted. On the basis of this information, the 10-fold *Pest Control Products Act* factor was reduced to 1-fold.

### 3.2 Acute Reference Dose (ARfD)

No acute endpoints of concern were identified in the toxicology database; therefore, an ARfD was not established.

### 3.3 Acceptable Daily Intake

To estimate risk of repeated dietary exposure, a no observed adverse effect level (NOAEL) of 27 mg/kg bw/day from the combined dietary chronic toxicity/carcinogenicity study in rats was selected for risk assessment. At the LOAEL of 135 mg/kg bw/day, decreased body weight and body weight gain and increased incidence of renal corticomedullary mineralization were observed in female rats. This study provides the lowest NOAEL in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. The composite assessment factor (CAF) is thus 100.

The Acceptable Daily Intake (ADI) is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{27\ \text{mg/kg bw/day}}{100} = 0.3\ \text{mg/kg bw/day of mandestrobin}$$

This ADI provides a margin of greater than 1500 to the dose resulting in increased incidence of benign ovary sex cord-stromal tumours in female rats and greater than 3300 to the dose resulting in increased incidence of fetal variations in the rat.

### Cancer Assessment

As previously discussed, an increase in benign sex cord-stromal tumours in females in the rat oncogenicity study with mandestrobin was considered equivocal based on the weight of evidence. Overall, the endpoints selected for the non-cancer risk assessment are protective of these equivocal findings.

## 3.4 Occupational and Residential Risk Assessment

### 3.4.1 Toxicological Endpoints

Occupational exposures to S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, S-2200 4 SC VPP Fungicide, and S-2200 3.2 FS Fungicide are characterized as short- to intermediate-term in duration and are predominantly by the dermal and inhalation routes.

#### 3.4.1.1 Short- and Intermediate-term Dermal

For short- and intermediate-term dermal risk assessment, the 28-day dermal toxicity study in rats was selected. No adverse effects were observed up to the limit dose of testing. A NOAEL of 1000 mg/kg bw/day was established.

The target margin of exposure (MOE) for these scenarios is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

#### 3.4.1.2 Short- and Intermediate-term Inhalation

For short- and intermediate-term inhalation scenarios, the reproductive toxicity study in rat was selected. For the inhalation scenarios, no repeat-dose inhalation toxicity study was available. Since an oral NOAEL was selected, an inhalation absorption factor of 100% was used in a route-to-route extrapolation. At the LOAEL of 166 mg/kg bw/day, increased brown pigmentation of the bile duct and periductular inflammatory cell infiltration in $F_1$ parental animals were observed. A NOAEL of 56 mg/kg bw/day was established.

The target MOE for these scenarios is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers. A *Pest Control Products Act* factor of 1-fold was applied for the reasons outlined in the *Pest Control Products Act* Hazard Characterization section.

#### 3.4.1.3 Non-dietary Oral Ingestion

For short-term incidental oral scenarios, the reproductive toxicity study in rat was selected. At the LOAEL of 166 mg/kg bw/day, increased brown pigmentation of the bile duct and periductular inflammatory cell infiltration in $F_1$ parental animals were observed. A NOAEL of 56 mg/kg bw/day was established.

The target MOE for this scenario is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers. A *Pest Control Products Act* factor of 1-fold was applied for the reasons outlined in the *Pest Control Products Act* Hazard Characterization section.

#### 3.4.1.4 Dermal Absorption

No in vivo or in vitro, rat or human, dermal absorption studies and/or data were submitted.

A dermal absorption value was not required for route-to-route extrapolation, as the NOAEL from the short-term 28-day dermal toxicity study is appropriate for assessing short- to intermediate-term exposures (no effects up to the limit dose of 1000 mg/kg bw/day).

### 3.4.2 Occupational Exposure and Risk

#### 3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Individuals have potential for exposure to S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, and S-2200 4 SC VPP Fungicide during mixing, loading and application (ground and aerial), and exposure to S-2200 3.2 FS Fungicide during treatment of seeds (including mixing, loading, treating, and handling of treated seeds including bagging, sewing and stacking). Dermal and inhalation exposure estimates for workers were generated from PHED and surrogate worker exposure studies and data belonging to exposure task forces (AHETF, ARTF, SEEDTROPEX, and ORETF).

Exposures to workers mixing, loading and applying S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, S-2200 4 SC VPP Fungicide, and S-2200 3.2 FS Fungicide are expected to be short- to intermediate-term duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for mixers/loaders/applicators applying S-2200 4 SC Fungicide or S-2200 4 SC Ag Fungicide to canola (representing Crop Group 20A (Rapeseed Subgroup)) using groundboom (open-cab), aerial, and sprinkler chemigation equipment; to grape (representing Crop Group 13-07F (Small fruit vine climbing subgroup except fuzzy kiwifruit)) using airblast (open-cab) and sprinkler chemigation equipment; and to strawberry (representing Crop Group 13-07G (Low growing berry subgroup)) using groundboom and sprinkler chemigation.

Exposure estimates were derived for mixers/loaders/applicators applying S-2200 4 SC Fungicide or S-2200 4 SC VPP Fungicide to turfgrass (golf courses, lawns and landscape areas around residential, institutional, public, commercial and industrial buildings, recreational areas and to sod (sod farms)) using groundboom, backpack, manually- and mechanically-pressurized handwands, and turf handgun equipment. The exposure estimates are based on mixers/loaders/applicators wearing a long-sleeved shirt, long pants, and chemical-resistant gloves for foliar and turf uses. In addition, mixers and loaders for aerial application wear coveralls.

Exposure estimates were derived for seed treaters (including treaters, baggers, and cleaners) applying S-2200 3.2 FS Fungicide to canola seeds (representing Crop Group 20A (Rapeseed Subgroup)) and corn seeds (field corn, sweet corn, and popcorn) using closed transfer commercial treating equipment; and to legume vegetable seeds (represented by soybean and pea seeds) using closed transfer commercial or open transfer on-farm treating equipment. The exposure estimates are based on treaters wearing a long-sleeved shirt, long pants, and chemical-resistant gloves with seed treatment equipment cleaners also wearing chemical-resistant coveralls.

Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted.

Dermal exposures were estimated by coupling the unit exposure values with the amount of product handled per day. Inhalation exposures were estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposures were normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the toxicological endpoints (NOAELs) to obtain the MOE; the target MOE is 100 for each of the dermal and inhalation routes. Routes of exposure cannot be combined since the toxic effects are different.

**Table 3.4-1 Estimated Exposures of Mixers, Loaders, and Applicators From Foliar Applications of S-2200 4 SC Fungicide to Canola (Subgroup 20A), Grapes (Subgroup 13-07F), Strawberry (Subgroup 13-07G), and Turfgrass and Sod**

| Scenario | Application rate (g a.i./ha) | ATPD (ha/day) | Amount of a.i. handled per day [1] (kg a.i./day) | PHED (unless otherwise stated) dermal (µg a.i./kg a.i. handled) | Dermal Exposure [2] (mg a.i./kg bw/day) | Dermal MOE [3] | PHED (unless otherwise stated) Inhalation (µg a.i./kg a.i. handled) | Inhalation Exposure [2] (mg a.i./kg bw/day) | Inhalation MOE [4] |
|---|---|---|---|---|---|---|---|---|---|
| **GROUND Applications** | | | | | | | | | |
| **Canola (covers strawberry (26 ha/day)): All Liquids Open M/L [7] (long pants, long sleeves, and gloves); Open cab groundboom (long pants, long sleeves, and no gloves)** | | | | | | | | | |
| Farmer M/L/A | 420 | 107 | 44.94 | 84.12 | 0.04725 | 21164 | 2.56 | 0.001438 | 38943 |
| Custom M/L/A | | 360 | 151.2 | 84.12 | 0.15899 | 6290 | 2.56 | 0.004838 | 11575 |
| **Grapes: All Liquids Open M/L (long pants, long sleeves, and gloves); open-cab airblast (long pants, long sleeves, and gloves)** | | | | | | | | | |
| Farmer, Custom M/L/A | 420 | 20 | 8.4 | 3820.44 [8] | 0.40115 | 2493 | 10.68 [8] | 0.001121 | 49955 |
| **Turfgrass and sod: Backpack equipment; All Liquids Open M/L/A (long pants, long sleeves, and gloves)** | | | | | | | | | |
| M/L/A | 472 | 0.1875 | 0.0885 | 5445.85 | 0.006020 | 166113 | 62.1 [8] | 0.0000689 | 782609 |

| Scenario | Application rate (g a.i./ha) | ATPD (ha/day) | Amount of a.i. handled per day [1] (kg a.i./day) | PHED (unless otherwise stated) dermal (µg a.i./kg a.i. handled) | Dermal Exposure [2] (mg a.i./kg bw/day) | Dermal MOE [3] | PHED (unless otherwise stated) Inhalation (µg a.i./kg a.i. handled) | Inhalation Exposure [2] (mg a.i./kg bw/day) | Inhalation MOE [4] |
|---|---|---|---|---|---|---|---|---|---|
| **Turfgrass and sod: Turf fumigant; All Liquids Open M/L/A (long pants, long sleeves, and gloves)** | | | | | | | | | |
| Custom M/L/A | 472 | 2 | 0.944 | 785 [c] | 0.00926 | 107991 | 4 [c] | 0.0000472 | 1186441 |
| **Turfgrass and sod: All Liquids Open M/L (long pants, long sleeves, and gloves); Open cab groundboom (long pants, long sleeves, and no gloves)** | | | | | | | | | |
| Golf course M/L/A | 472 | 16 | 7.552 | 64.12 | 0.007940 | 125945 | 2.56 | 0.0002512 | 223180 |
| Sod farm M/L/A | | 30 | 14.16 | 64.12 | 0.01489 | 67159 | 2.56 | 0.0004698 | 119205 |
| **Turfgrass and sod: Mechanically pressurized handgun; All Liquids Open M/L/A (long pants, long sleeves, and gloves)** | | | | | | | | | |
| Custom M/L/A | 472 | 4.75 [d] | 2.242 | 5585.49 | 0.15653 | 6389 | 151 | 0.004232 | 12766 |
| **AERIAL (canola only): All Liquids Open M/L (coveralls, long pants, long sleeves, and gloves); Applicator (long pants, long sleeves, and no gloves)** | | | | | | | | | |
| Farmer, Custom M/L | 420 | 400 | 168 | 32.77 | 0.06882 | 14531 | 1.6 | 0.003360 | 16667 |
| Farmer, Custom A | | 400 | 168 | 9.66 | 0.02029 | 49285 | 0.07 | 0.000147 | 380952 |
| **CHEMIGATION (canola, grapes, strawberry): All Liquids Open M/L (long pants, long sleeves, and gloves)** | | | | | | | | | |
| Sprinkler Chemigation M/L | 420 | 140 | 58.8 | 51.10 | 0.03755 | 26631 | 1.6 | 0.001176 | 47619 |

1. Amount of a.i. handled per day calculated using the maximum application rate × ATPD
2. Exposure was calculated using the amount of a.i. handled per day × unit exposure value/body weight (80 kg) (dermal or inhalation). No dermal absorption value required; assumed 100% inhalation systemic absorption
3. Estimates of dermal exposure for M/L and A were compared to a dermal NOAEL of 1000 mg/kg bw/day, target MOE = 100.
4. Estimates of inhalation exposure for M/L and A were compared to a NOAEL of 56 mg/kg bw/day, target MOE = 100.
5. Farmer mixer/loader is sufficient to represent the expected exposures of workers for chemigation

a. Moderate inhalation rate

b. Revised open-cab airblast unit exposures

c. ORETF (commercial) professional low pressure nozzle gun sprayer. 1000L/day default volume per day ÷ (min. 2.1 L spray volume/100 m² × 10000 m²/ha)

### Table 3.4-2 Risk Estimates for Workers Treating Seeds in Commercial Facilities with S-2200 3.2 FS Fungicide

| Worker task | Unit exposure (µg/kg a.i. handled)[1] | | Appl. rate | Seed treated (kg seed/day)[2] | Dermal Exposure (mg/kg bw/day)[3] | Dermal MOE[4] | Inhalation (mg/kg bw/day)[3] | Inhalation MOE[4] |
|---|---|---|---|---|---|---|---|---|
| | Dermal | Inhalation | (kg a.i./kg seed) | | | | | |
| **Closed mix, load, transfer commercial facilities** | | | | | | | | |
| **Corn (field, sweet, and pop)** | | | | | | | | |
| Treater | 0.88 | 0.016 | 0.00006 | 125,000 | 8.25E-05 | 1.21E+07 | 1.50E-06 | 3.73E+07 |
| Bagger | 17.67 | 0.89 | 0.00006 | 125,000 | 1.66E-03 | 6.02E+05 | 8.34E-05 | 6.71E+05 |
| Cleaner (normalized)[5] | 17.1 | 5.1 | 0.00006 | - | 1.29E-03 | 7.75E+05 | 3.83E-04 | 1.46E+05 |
| Treater + Cleaner [5] | - | - | 0.00006 | - | 1.37E-03 | 7.30E+05 | 3.85E-04 | 1.45E+05 |
| **Canola** | | | | | | | | |
| Treater | 0.88 | 0.016 | 0.0001 | 67,000 | 7.37E-05 | 1.36E+07 | 1.34E-06 | 4.18E+07 |

| Worker task | Unit exposure (µg/kg a.i. handled)[1] |  | Appl. rate | Seed treated (kg seed/day)[3] | Dermal Exposure (mg/kg bw/day)[4] | Dermal MOE[5] | Inhalation (mg/kg bw/day)[4] | Inhalation MOE[5] |
|---|---|---|---|---|---|---|---|---|
|  | Dermal | Inhalation | (kg a.i./kg seed) |  |  |  |  |  |
| Bagger | 17.67 | 0.89 | 0.0001 | 67,000 | 1.48E-03 | 6.76E+05 | 7.45E-05 | 7.52E+05 |
| Cleaner (normalized)* | 17.1 | 5.1 | 0.0001 | - | 2.15E-03 | 4.65E+05 | 6.38E-04 | 8.78E+04 |
| Treater + Cleaner ¶ | - | - | 0.0001 | - | 2.22E-03 | 4.50E+05 | 6.39E-04 | 8.76E+04 |
| Soybean |  |  |  |  |  |  |  |  |
| Treater | 0.88 | 0.016 | 0.0001 | 63,000 | 6.93E-05 | 1.44E+07 | 1.26E-06 | 4.44E+07 |
| Bagger | 17.67 | 0.89 | 0.0001 | 63,000 | 1.39E-03 | 7.19E+05 | 7.01E-05 | 7.99E+05 |
| Cleaner (normalized)* | 17.1 | 5.1 | 0.0001 | - | 2.15E-03 | 4.65E+05 | 6.38E-04 | 8.78E+04 |
| Treater + Cleaner ¶ | - | - | 0.0001 | - | 2.22E-03 | 4.50E+05 | 6.39E-04 | 8.76E+04 |
| Legumes (other than soybean) |  |  |  |  |  |  |  |  |
| Treater | 0.88 | 0.016 | 0.0001 | 216,000 | 2.38E-04 | 4.21E+06 | 4.32E-06 | 1.30E+07 |
| Bagger | 17.67 | 0.89 | 0.0001 | 216,000 | 4.77E-03 | 2.10E+05 | 2.40E-04 | 2.33E+05 |
| Cleaner (normalized)* | 17.1 | 5.1 | 0.0001 | - | 2.15E-03 | 4.65E+05 | 6.38E-04 | 8.78E+04 |
| Treater + Cleaner ¶ | - | - | 0.0001 | - | 2.39E-03 | 4.19E+05 | 6.42E-04 | 8.72E+04 |

* Normalized Cleaner unit exposure (µg/g a.i./100kg seed/day)
= 240.02 µg/day / 14.04 g a.i./100 kg seed, application rate in the exposure study
¶ Assuming that a worker both treats and cleans in the same workday; using normalized cleaner, and considered conservative
1. For closed transfer commercial facilities, the arithmetic mean values were used from the surrogate exposure study; long-sleeved shirt and long pants (plus nitrile gloves for mixer/loader/calibrators), plus Tyvek coveralls and nitrile gloves for cleaners
2. Highest PMRA-supported application rate on the label
3. Default seed treatment throughput for beans (PMRA seed treatment database)
4. Exposure (mg/kg bw/day) = unit exposure (µg/kg a.i. handled) × application rate (g a.i./100 kg seed) × seeds treated (kg seed/day) × 0.001(mg/µg) / body weight (kg bw)
Cleaner Normalized Exposure (mg/kg bw/day) = (unit exposure (µg/g a.i./100 kg seed) × (0.0001 or 0.00000[illegible]) kg a.i./kg seed × 100 kg seed × 1000 g/kg)/(80 kg bw × 1000 µg/mg))
5. Margin of Exposure (MOE) = NOAEL/Exposure; NOAEL = 1000 mg/kg bw/day, target MOE = 100; inhalation NOAEL = 56 mg/kg bw/day, target MOE = 100

## Table 3.4-3 Risk Estimates for On-Farm Treatment (Mobile Treaters) of Legume Seeds with S-2200 3.2 FS Fungicide

| Unit exposure values [1,2] (µg/kg a.i.) |  | Amount of a.i. handled per day [3] (kg a.i./day) | Dermal Exposure [4,5] (mg/kg bw/day) | Dermal MOE [6] | Inhalation Exposure [4,5] (mg/kg bw/day) | Inhalation MOE [6] |
|---|---|---|---|---|---|---|
| Dermal | Inhalation |  |  |  |  |  |
| 90th percentile | 90th percentile |  |  |  |  |  |
| 140.9 | 7.825 | 1.9 | 0.003346 | 298828 | 0.000186 | 301345 |

1. Surrogate mixer/loader/applicator study
2. Workers wearing a single layer (a long-sleeved shirt, long pants, and chemical-resistant gloves)
3. Amount a.i. handled per day based on peas (except cowpea and field pea representing legumes, including soybeans) = application rate (0.0001 kg a.i./kg seed) × seeding rate (190 kg seed/ha) × area planted per day (100 ha/day)
4. No adjustment for dermal absorption required; both dermal and inhalation exposures considered 100% systemically available
5. Daily exposure (mg/kg bw/day)
= (Unit exposure × Amount of a.i. handled/day) / (80 kg bw × 1000 µg/mg)
6. Margin of Exposure (MOE) = NOAEL (route-specific)/Exposure; short- to intermediate-term durations, target MOE = 100

**Table 3.4-4 Exposure and Risk Estimates for Farmers Treating and Planting Legume Seeds with S-2200 3.2 FS Fungicide**

| PPE: single layer + chemical-resistant gloves | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Crop | Unit exposure (µg/kg bw/day)[1] | | Seed treated and Planted[2] (kg seed/day) | Rate (kg a.i./kg seed) | Dermal Exposure[3] (mg/kg bw/day) | Dermal MOE (target = 100)[4] | Inhalation Exposure[3] (mg/kg bw/day) | Inhalation MOE (target = 100)[4] |
| | Dermal | Inhalation | | | | | | |
| Legume vegetable seeds | 407.10 | 223.03 | 19000 | 0.0001 | 0.0006785 | 103766 | 0.0005297 | 10573 |

[1] Unit exposures in the surrogate seed treatment study for workers wearing a long-sleeved shirt, long pants, and chemical-resistant gloves

[2] From the Seed Treated/Planted Per Day tables (2009)

[3] Exposure = (Unit exposure × Seed treated/planted × Rate)/(1000 µg/mg × 80 kg bw)

[4] Dermal NOAEL = 1000 mg/kg bw/day, target MOE = 100; inhalation NOAEL = 56 mg/kg bw/day, target MOE = 100

### 3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposure to workers re-entering areas treated with S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, S-2200 4 SC VPP Fungicide, and workers planting seeds treated with S-2200 3.2 FS Fungicide. Given the nature of activities performed, the primary route of exposure for workers re-entering treated areas would be through the dermal route, and through the dermal and inhalation routes for planting treated seeds. The durations of exposure are considered to be short-term in duration when entering treated crops, turf, and handling and planting seeds.

Dermal exposures to workers entering treated areas (Table 3.4-5) are estimated by coupling dislodgeable foliar residue values for foliar treatments, or turf transferable residue values for turf, with activity-specific transfer coefficients. Chemical-specific dislodgeable foliar residue data were not submitted. Therefore, a default dislodgeable foliar residue value of 25%, or default turf transferable residue value of 1% of the application rate on the day of the final treatment, was used in the exposure assessment.

Dermal and inhalation exposures of workers planting treated seeds (Table 3.4-4) are estimated by coupling unit exposures for planting treated seeds with the amount of seeds planted, and size of areas planted.

No dermal absorption value was required since the dermal endpoint was based on a dermal study. Inhalation absorption is considered 100%. Exposures were normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the toxicological end point to obtain the MOE; the target MOE is 100.

### Table 3.4.5 Postapplication Occupational Exposure and Risk Estimates for Re-Entry Tasks Performed in Crops Treated with S-2200 4 SC Fungicide

| Crop | Task | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | MOE |
|---|---|---|---|---|---|---|---|---|
| Canola | [illegible] | [illegible] | [illegible] | — | [illegible] | [illegible] | [illegible] | [illegible] |
| Grape | [illegible] | [illegible] | [illegible] | 10 | [illegible] | [illegible] | [illegible] | [illegible] |
| | [illegible] | [illegible] | [illegible] | 10 | [illegible] | [illegible] | [illegible] | [illegible] |
| Strawberry | Hand harvesting | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] |
| Turfgrass/ Sod | [illegible] | [illegible] | [illegible] | 10 | [illegible] | [illegible] | [illegible] | [illegible] |
| | [illegible] | | | | | [illegible] | [illegible] | [illegible] |
| | [illegible] | | | | | [illegible] | [illegible] | [illegible] |
| | [illegible] | | | | | [illegible] | [illegible] | [illegible] |

[illegible]

### Table 3.4.6 Exposure and Risk Estimates for Planting Canola, Corn, Soybean, and Pea Seeds Treated with S-2200 3.2 FS Fungicide

| Scenario | [illegible] | | [illegible] | [illegible] | [illegible] | [illegible] | | MOE | MOE |
|---|---|---|---|---|---|---|---|---|---|
| Planting | Dermal | Inhalation | | | [illegible] | Dermal | Inhalation | Dermal | Inhalation |
| canola | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] |
| corn | | | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] |
| [illegible] | | | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] |
| soybean | | | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] |

[illegible]

Risks to workers entering treated crops, turfgrass and sod, are not of concern. The default restricted entry interval (REI) of 12 hours is adequate to protect workers. Risks to workers planting treated seeds are not of concern when following the treated seed label precautions.

### 3.4.3 Residential Exposure and Risk Assessment

#### 3.4.3.1 Handler Exposure and Risk

No homeowner applicator scenario is proposed.

#### 3.4.3.2 Postapplication Exposure and Risk

##### 3.4.3.2.1 Postapplication Dermal Exposures

Section 3, Lawns and Turf, of the 2012 United States Environmental Protection Agency (USEPA) Residential Standard Operating Procedure (SOP) was used to determine postapplication exposures to people re-entering treated lawns in residential areas.

The duration of exposure is considered to be short-term (up to 30 days) for golfing and for residential turf activities. No product-specific turf transferable residue (TTR) study was provided; therefore, the current default peak (day 0) DFR value of 1% of the application rate, transfer coefficients, exposure time, and algorithms were based on the SOP for turf. Body weights used were 80 kg for adults, 57 kg for youth, 32 kg for children (6<11years old), and 11 kg for children (1<2 years old).

**Table 3.4-7 Postapplication Dermal Exposure and Risk Estimates for Re-Entry onto Turf Treated with S-2200 4 SC Fungicide**

| Lifestage (years of age) | TTR, (μg/cm$^2$) | Transfer Coefficient (cm$^2$/hour) | Hours of Exposure (hour/day) | Exposure (mg/day) | Absorbed Dose (mg/kg/day) | Dermal MOE |
|---|---|---|---|---|---|---|
| **High Contact Lawn Activities** | | | | | | |
| Adult 18+ | 0.05 | 180,000 | 1.5 | 12.74 | 0.1593 | 6277 |
| Youth 11 <16 | | 148,000 | 1.3 | 9.08 | 0.1593 | 6277 |
| Children 1 <2 | | 49,000 | 1.5 | 3.47 | 0.3154 | 3171 |
| **Mowing Turf** | | | | | | |
| Adult 18+ | 0.05 | 5,500 | 1 | 0.2596 | 0.003245 | 308166 |
| Youth 11 <16 | | 4,500 | 1 | 0.2124 | 0.003726 | 268362 |
| **Golfing (Treated greens, tees, and fairways)** | | | | | | |
| Adult 18+ | 0.05 | 5,300 | 4 | 1.0006 | 0.012508 | 79949 |
| Youth 11 <16 | | 4,400 | 4 | 0.8307 | 0.01457 | 68615 |
| Children 6 <11 | | 2,900 | 4 | 0.5475 | 0.01711 | 58445 |

#### 3.4.3.2.2 Child Incidental Oral Ingestion

A child may place a hand in his/her mouth a number of times, as well as place an object in their mouth a number of times during a certain period of time. Each of these events could result in a potential transfer of residue, but could also result in a soil ingestion event as soil may be present on the hand or object during mouthing (USEPA Residential SOP 2012). Table 3.4-8 shows estimates of the exposures for each scenario. Risks from each of the three non-dietary oral ingestion scenarios are considered not to be of concern (greater than the target MOE of 100).

**Table 3.4-8 Postapplication Residential Child Oral Exposure and Risk Assessment for Entry onto Turfgrass Treated with S-2200 4 SC Fungicide**

| Lifestage (years of age) | Route of ingestion | Residue loading (mg/cm²) | Oral Exposure (mg/kg bw/day) | MOE |
|---|---|---|---|---|
| Children 1 <2 | Hand-to-mouth | 0.00069 | 0.0065 | 8660 |
| | Object-to-mouth | 0.04720 | 0.00020 | 285171 |
| | Incidental soil ingestion | 3.1624 (µg/g) | 1.4E-05 | 3.9E+06 |

#### 3.4.3.2.3 Residential Aggregate Assessment

Adults and youth are considered to conduct multiple postapplication activities on treated turf. The public (including children) may enter treated recreational turf areas on the day of treatment. Table 3.4-9 shows the activities that are considered to co-occur when adults and youth are active on treated turf. Golfing is not part of the aggregate assessment. Risks for adults and youth are not considered to be of concern (greater than the target MOE of 100).

**Table 3.4-9 Residential Dermal Aggregate Risks of Entry onto Turfgrass Treated with S-2200 4 SC Fungicide (or S-2200 4 VPP Fungicide)**

| | Scenario | | Dermal MOE |
|---|---|---|---|
| | Absorbed Dose (mg/kg bw/day) | | |
| Lifestage (years of age) | High Contact Lawn Activities [1] | Mowing Turf [1] | Aggregate [2] |
| Adult 18+ | 0.1593 | 0.003245 | 6154 |
| Youth 11 <16 | 0.1593 | 0.003726 | 6135 |

1. Exposures taken from Table 3.4-7
2. Based on SPN2003-04; target MOE is 100

Postapplication exposure scenarios that are likely to co-occur over a short term are the dermal and hand-to-mouth scenarios (2012, USEPA Residential SOP, Turf and Lawns) (Table 3.4-10). However, there is no common toxic effect for aggregation of dermal and oral exposures; therefore, the dermal route is not included. The PMRA also includes dietary exposure in this aggregate because these exposures are by the oral route. Aggregate oral exposure risks to children are not considered to be of concern.

**Table 3.4-10 Aggregate Oral (Non-Dietary and Dietary) Ingestion of Mandestrobin Residues by Children 1<2 yrs**

| Route of ingestion | Oral Exposure (mg/kg bw/day) |
|---|---|
| Hand-to-mouth [1] | 0.0065 |
| Chronic dietary exposure [2] | 0.027593 |
| Aggregate MOE [3] (target = 100) | 1644 |

1. From Table 3.4-8; hand-to-mouth activity is not expected to under-estimate non-dietary intake of children 1<2 years of age
2. From Dietary Exposure Assessment (food + water)
3. Using PMRA SPN2003-04

#### 3.4.3.2.4 Pick-Your-Own Acute Aggregate Exposure Assessment

Strawberry and lowbush blueberry are considered to be pick your own (PYO) crops. The public may be exposed to residues of S-2200 4 SC Fungicide on these crops at PYO operations. This exposure is expected to be acute and to occur by the dermal and oral routes. The acute dermal exposures for adults, youth, and children in PYO facilities are addressed by the dermal exposures of workers re-entering treated fields for hand harvesting, and not considered to be of concern. Exposure by the oral route is addressed by the dietary exposure assessment. Therefore, the public picking strawberries and lowbush blueberries at PYO facilities is acceptable at the pre-harvest interval on the label.

### 3.4.3.3 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Application is limited to agricultural crops only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

## 3.5 Food Residues Exposure Assessment

### 3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in plant products is mandestrobin. The data gathering/enforcement analytical method is valid for the quantitation of mandestrobin (S-2200) residues in crops. The residue definition for risk assessment and enforcement in animal commodities will be determined once a livestock feeding study and enforcement method are submitted to the Agency.

The residues of mandestrobin are stable in rapeseed (seed, oil and meal), lettuce, barley (grain, straw), soybean seed, and corn (grain, forage, K+CWHR) for up to 12 months; in corn stover for up to 9 months; in grapes for up to 8 months; in grape juice for up to 7 months; and in strawberries and raisins for up to 5 months, when stored in a freezer at -18°C. Freezer storage stability studies are on-going for rapeseed (seed, oil, and meal), strawberries and grapes (fruit, raisins). Mandestrobin residues concentrated in the following processed commodities: raisin (1.9-fold), and grape juice (1.4-fold). Quantifiable residues are not expected to occur in livestock matrices with the current use pattern. Crop field trials conducted throughout Canada and the United States using end-use products containing mandestrobin at approved rates in or on corn, grapes, rapeseed, soybeans, and strawberries are sufficient to support the proposed maximum residue limits.

### 3.5.2 Concentrations in Drinking Water

Estimated environmental concentrations (EECs) of mandestrobin combined residue in potential drinking water sources (groundwater and surface water) were generated using computer simulation models. An overview of how the EECs are estimated is provided in the PMRA's Science Policy Notice SPN2004-01, *Estimating the Water Component of a Dietary Exposure Assessment*. EECs of mandestrobin in groundwater were calculated using the PRZM-GW model to simulate leaching through a layered soil profile over a 50-year period. The concentrations calculated using PRZM-GW are average concentrations in the top one metre of the water table. EECs of mandestrobin combined residue in surface water were calculated using the SWCC model, which simulates pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. Pesticide concentrations in surface water were estimated in a vulnerable drinking water source, a small reservoir.

Drinking water modelling of mandestrobin includes four transformation products, 5-COOH-S-2200, MCBX, S-2200-OR and S-2200-ORC as well as mandestrobin itself. Degradation rates for drinking water modelling were calculated from the overall degradation of these five compounds, and for groundwater modelling, the more conservative $K_d$ from 5-COOH-S-2200 was used.

A Level 1 drinking water assessment was conducted using conservative assumptions with respect to environmental fate, application rate and timing, and geographic scenario. The Level 1 EEC estimate is expected to allow for future use expansion into other crops at this application rate. Table 3.5-1 lists the application information and main environmental fate characteristics used in the simulations. Twenty-seven initial application dates between May and September were modelled. The model was run for 50 years for all scenarios. The largest EECs of all selected runs are reported in Table 3.5-2 below.

**Table 3.5-1 Major groundwater and surface water model inputs for Level 1 assessment of mandestrobin**

| Type of Input | Parameter | Value |
|---|---|---|
| Application Information | Crop(s) to be treated | Beans, Blueberries, Canola, Chick peas, Corn, Flaxseed, Gooseberries, Grapes, Lentils, Lupins, Mustard seed, Peas, Radish, Soybeans, Strawberries, Turf |
| | Maximum allowable application rate per year (g a.i./ha) | 1890 |
| | Maximum rate each application (g a.i./ha) | 472 (turf) and 420 (for other crops) |
| | Maximum number of applications per year | 4 |

| Type of Input | Parameter | Value |
|---|---|---|
|  | Minimum interval between applications (days) | 14 (turf) and 7 (for other crops) |
|  | Method of application | Field sprayer or aerial application equipment |
| Environmental Fate Characteristics | Hydrolysis half-life at pH 7 (days) | stable |
|  | Photolysis half-life in water (days) | 4.5 days (mandestrobin only)<br>10.7 days (mandestrobin with four transformation products) |
|  | Adsorption $K_{OC}$ or $K_d$ (mL/g) | Mandestrobin $K_{OC}$ of 365 used for surface water modelling; 5-COOH-S2200 $K_d$ of 1.24 used for groundwater modelling |
|  | Aerobic soil biotransformation half-life (days) | 264 days @ 20°C for eco<br>306 days @ 20°C for drinking water |
|  | Aerobic aquatic biotransformation half-life (days) | 693 days @ 20°C for eco<br>4320 days @ 20°C for drinking water |
|  | Anaerobic aquatic biotransformation half-life (days) | 2345 days @ 20°C for eco<br>6335 days @ 20°C for drinking water |

**Table 3.5-2 Level 1 estimated environmental concentrations of mandestrobin in potential drinking water sources**

| Compound | Groundwater EEC (µg a.i./L) |  | Surface Water EEC (µg a.i./L) |  |
|---|---|---|---|---|
|  |  |  | Reservoir |  |
|  | Daily[1] | Yearly[2] | Daily[3] | Yearly[4] |
| Mandestrobin combined residue | 225 | 225 | 82 | 21 |

Notes:

[1] 90th percentile of daily average concentrations

[2] 90th percentile of 365 day moving-average concentrations

[3] 90th percentile of the peak concentrations from each year

[4] 90th percentile of yearly average concentrations

### 3.5.3 Dietary Risk Assessment

Chronic (non-cancer) dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™ NHANES, Version 4.02), which incorporates food consumption data from the National Health and Nutritional Examination Survey, What We Eat in America (NHANES/ WWEIA) dietary survey for the years 2003-2008 available through CDC's National Center for Health Statistics (NCHS).

#### 3.5.3.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the basic chronic non-cancer analysis for mandestrobin: 100% crop treated, default processing factors and proposed MRLs of rapeseed (CSG 20A), grape (CSG 13-07F), strawberry (CSG 13-07G, except cranberry), soybean (CG 6, except cowpea and field pea) and corn. The basic chronic dietary exposure from all supported mandestrobin food uses (alone) for the total population, including infants and children, and all representative population subgroups is less than 1.3% of the acceptable daily intake (ADI). Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to mandestrobin from food and drinking water is 2.8% (0.0084 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for children 1-2 years old at 9.2% (0.028 mg/kg bw/day) of the ADI.

#### 3.5.3.2 Acute Dietary Exposure Results and Characterization

No appropriate endpoint attributable to a single dose for the general population (including children and infants) was identified.

### 3.5.4 Aggregate Exposure and Risk

The aggregate risk for mandestrobin consists of exposure from food and drinking water sources.

### 3.5.5 Maximum Residue Limits

**Table 3.5-3 Proposed Maximum Residue Limits**

| Commodity | Recommended Maximum Residue Limit (ppm) |
|---|---|
| Raisins | 7.0 |
| Small fruit vine climbing (Crop Subgroup 13-07F, except fuzzy kiwifruit) | 5.0 |
| Low growing berry (Crop Subgroup 13-07G, except cranberry) | 3.0 |
| Rapeseed (Crop Subgroup 20A) | 0.5 |
| Legume vegetables (succulent or dried) (Crop Group 6, except cowpea and field pea), corn (field, popcorn, sweet) | 0.02 |

Maximum Residue Limits (MRLs) are proposed for each commodity included in the listed crop groupings in accordance with the Residue Chemistry Crop Groups webpage in the Pesticides and Pest Management section of Health Canada's website.

For additional information on maximum residue limits in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in animal and plant matrices, analytical methodologies, field trial data, and acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1, 8 and 9.

## 4.0 Impact on the Environment

The active substance mandestrobin is a racemic mixture of the two isomers (S-2200 *R*-isomer and S-2200 *S*-isomer) in a ratio of 50:50. The results presented in this section are for the mixture unless stated otherwise.

### 4.1 Fate and Behaviour in the Environment

The fate and behaviour of mandestrobin and its major transformation products are summarized in Appendix I, Table 10. The chemical name and structure of transformation products formed in the environment, as well as a summary of their occurrence in environmental fate studies, are presented in Appendix I, Table 11.

Mandestrobin is introduced in the environment when it is applied as a seed treatment, foliar spray and chemigation to a variety of seeds, field crops and non-crops. Mandestrobin could reach the soil upon application or through wash-off from the leaves. Abiotic transformation processes are not expected to contribute significantly to the dissipation of mandestrobin in soil as this compound is stable to hydrolysis and phototransformation. Biotransformation may be an important route of dissipation for mandestrobin in the terrestrial environment.

In both aerobic and anaerobic soils, mandestrobin transformed to the major products 5-COOH-S-2200, DX-CA-S-2200, 2-CONH$_2$-S-2200, 5-CONH$_2$-S-2200, MCBX and De-Xy-S-2200. Mandestrobin is slightly persistent to persistent in aerobic soil and will also persist in anaerobic soil.

Based on results from adsorption studies, mandestrobin exhibited medium to low mobility in soil, transformation products 5-COOH-S-2200 and 2-COOH-S-2200 exhibited very high to low mobility. The groundwater ubiquity scores (GUS) calculated for mandestrobin and its transformation products 5-COOH-S-2200 and 2-COOH-S-2200 based on their persistence and mobility indicate that mandestrobin is a borderline leacher and that 5-COOH-S-2200 and 2-COOH-S-2200 are probable leachers. In field dissipation studies, no residues of mandestrobin and its transformation products were detected beyond a 30 cm soil depth. Mandestrobin will not carry over to the next growing season.

Mandestrobin could reach surface water through spray drift and runoff. Once in the aquatic environment, mandestrobin is not expected to hydrolyze, but will undergo rapid phototransformation in clear shallow water to the major transformation products S-2200-OR, S-2200-ORC, S-2200-PR and CO$_2$. Biotransformation is not a primary route of transformation for mandestrobin in water and large amounts of mandestrobin were shown to partition into sediment. MCBX and 5-COOH-S-2200 were the only major biotransformation products identified in aquatic systems. Mandestrobin does not accumulate to a large degree in fish and depuration occurs rapidly.

Residues of mandestrobin and its transformation products are not expected to be found in air. Mandestrobin exhibits low volatility based on its low vapour pressure.

### 4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental concentrations are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are derived using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats, including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1 in most cases except for bees and certain beneficial arthropods where the level of concern is 0.4 and 2, respectively). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

#### 4.2.1 Risks to Terrestrial Organisms

A risk assessment for mandestrobin and its transformation products was undertaken for terrestrial organisms based on available toxicity data. A summary of terrestrial toxicity data is presented in Appendix I, Table 12. Results of the accompanying risk assessment are presented in Appendix I, Tables 13-15.

**Earthworms:** Earthworms could be exposed to mandestrobin when this compound reaches the soil upon application. The expected environmental concentration is, therefore, calculated based on a direct application of mandestrobin to bare soil at the maximum seasonal labelled application rate.

At levels higher than those expected in the Canadian environment, the acute exposure of earthworms to mandestrobin has been shown to cause mortality and decreased weight. Chronic exposure to mandestrobin also resulted in significant reduction in reproduction and body weight. However, given the low expected environmental concentration, risk quotients calculated for acute and chronic exposure to mandestrobin do not exceed the level of concern. The 5-COOH-S-2200 and 2-COOH-S-2200 transformation products were not acutely toxic to earthworms. There is therefore no concern from acute exposure to these transformation products.

**Bees (pollinators):** Foraging bees could be exposed directly to mandestrobin spray droplets during application or to mandestrobin residues found on the surface of leaves (contact exposure). Foraging bees could also be exposed to mandestrobin through the ingestion of pollen and nectar contaminated from direct spray or the systemic movement in the plant (oral exposure). In addition, brood may be exposed to mandestrobin and its transformation products as foraging bees bring contaminated pollen and nectar back to the hive.

In laboratory tests, mandestrobin was non-toxic to adult honey bees when applied directly on bees or through diet consumption. When honey bee larvae were incubated with a diet treated with mandestrobin, no mortality was observed at the highest dose tested. All risk quotients calculated for mandestrobin did not exceed the level of concern.

**Beneficial arthropods:** The risk assessment for beneficial arthropods considers that the main route of exposure for these non-target organisms is from contact with treated plant material both on the treated area (from direct spray on the crop) and at the margins of the treated field (from spray drift). The expected concentration of mandestrobin residues on foliage within the treated field is calculated as the cumulative application rate, which takes into account the maximum labelled application rate, the application interval and the dissipation of the compound on the surface of the leaves.

In laboratory tests carried out with freshly dried residues on a glass plate, S-2200 25SC Fungicide caused no statistically significant adverse acute effects on the parasitic wasp and predatory mite. Significant effects on the reproduction of the parasitic wasp were observed, but at levels higher than those expected in the environment. The screening level risk quotients calculated for both the predatory mite and the parasitic wasp were below the level of concern.

**Birds and mammals:** At the highest dose, acute oral exposure to mandestrobin caused no mortality in bobwhite quail and canary. When mandestrobin was administered in the diet no adverse effects to bobwhite quail and mallard duck were observed. In reproductive tests, no subchronic or reproductive effects were observed at the highest concentrations tested for either bobwhite quail or mallard duck.

Laboratory studies indicated that mandestrobin was not acutely toxic to rats. Among chronic effects observed in a two-generation dietary reproduction study with rats, was a decreased body weight in offspring.

For birds and mammals, risk quotients calculated at the screening level for mandestrobin did not exceed the level of concern on an acute or reproductive basis for both foliar application (up to 4 times a year for a maximum total rate of 1888 g a.i./ha/year) and seed treatment (up to 10 g a.i./100 kg seeds or 0. 9 g ai/ha).

**Non-target plants:** For the risk assessment, the cumulative application rate is compared to plant toxicity endpoints. The cumulative application rate takes into account the maximum labelled application rate, the application interval and the dissipation of the compound on the surface of the leaves. For the off-field assessment, the rate is adjusted according to the projected drift deposition at one metre downwind from the site of application.

The toxicity of S-2200 4 SC Fungicide to non-target plants was determined through vegetative vigour and seedling emergence assays using standard crop species. No significant adverse effects were observed in any plant species at the highest application rate tested (560 g a.i./ha). However, given that the study was conducted at the one-time application rate of 560 g a.i./ha, whereas the seasonal maximum application rate (4 × 472 g a.i./ha) is 1888 g a.i./ha, the screening risk quotient exceeded the level of concern. The risk to terrestrial plants was, thus, further assessed.

For an ASAE (American Society of Agricultural Engineers) 'coarse' droplet size, the maximum spray drift deposition at one metre downwind from the point of application is 17% for aerial application. Based on the risk quotients using the off-field EECs from drift, the level of concern for terrestrial vascular plants is not exceeded.

There is still uncertainty with regards to potential effects on the vegetative vigour and seedling emergence of plants after exposure to multiple applications. Due to this uncertainty, it was determined that drift mitigation measures are necessary.

### 4.2.2 Risks to Aquatic Organisms

A risk assessment of mandestrobin, its *R*- and *S*-isomers and transformation products 2-COOH-S-2200, 5-COOH-S-2200, S-2200-OR and S-2200-ORC was undertaken for freshwater and marine organisms based on available toxicity data. A summary of aquatic toxicity data is presented in Appendix I, Table 16. The accompanying risk assessment is presented in Appendix I, Tables 17-20.

**Freshwater invertebrates:** Mandestrobin was moderately toxic and S-2200 *R*-isomer was highly toxic to daphnids on an acute basis. Acute exposure to S-2200 *S*-isomer and other transformation products did not affect daphnids. In general, the *S*-isomer was shown to be of lower toxicity to aquatic organisms than mandestrobin, while the *R*-isomer was shown to be of comparable toxicity. Chronic exposure to mandestrobin reduced parental survival, reproduction and growth in daphnids, reduced the survival in chironomids, and reduced body length in amphipods.

The screening level risk quotients for freshwater invertebrates from acute and chronic exposure to mandestrobin do not exceed the level of concern. The risk quotients for daphnids from acute exposure to S-2200 *R* and *S*-isomers and the transformation products, 2-COOH-S-2200, 5-COOH-S-2200, S-2200-OR and S-2200-ORC do not exceed the level of concern at the screening level.

**Freshwater fish:** Mandestrobin was demonstrated to be of moderate toxicity to bluegill sunfish and sheepshead minnow, but showed high toxicity to rainbow trout and fathead minnow. The S-2200 *R*-isomer was highly toxic to rainbow trout on an acute basis. Acute exposure to S-2200 *S*-isomer and other transformation products did not affect rainbow trout.

The risk quotients for rainbow trout resulting from acute exposure to S-2200 *S*-isomer and transformation products 2-COOH-S-2200, 5-COOH-S-2200, S-2200-OR did not exceed the level of concern at the screening level. The screening level risk quotients for freshwater fish resulting from acute and chronic exposure to mandestrobin, and from acute exposure to S-2200 *R*-isomer and S-2200-ORC exceeded the level of concern. The risk to freshwater fish from acute and chronic exposure to mandestrobin, S-2200 *R*-isomer and S-2200-ORC was further assessed (see Section 4.2.3).

**Amphibians:** To assess the risk to amphibians, fish toxicity endpoints are used as surrogate data, when amphibian data are not available, to represent aquatic life-stages of amphibians. The difference between fish and amphibian risk assessments is related to the water depth used for the estimated environmental concentrations (water depth of 15 cm for amphibians). The screening level risk quotients for acute and chronic exposures of amphibians to mandestrobin exceeded the level of concern. The risk to amphibians was thus further assessed (see Section 4.2.3).

**Freshwater algae and vascular plants:** Mandestrobin showed adverse effects on cell density, growth rate and yield in green algae, blue-green algae and diatoms. S-2200 *R*-isomer and 2-COOH-S-2200 reduced the growth rate and biomass in test with green algae. S-2200 *S*-isomer and other transformation products had no adverse affects on green algae. Mandestrobin reduced the frond number and biomass of duckweed.

The risk quotient for freshwater algae resulting from acute exposure to mandestrobin and the S-2200 *R*-isomer exceeded the level of concern at the screening level. The risk quotients for freshwater green alga from exposure to S-2200 *S*-isomer and the transformation products 2-COOH-S-2200, 5-COOH-S-2200, S-2200-OR and S-2200-ORC did not exceed the level of concern at the screening level. The risk quotient for duckweed from exposure to mandestrobin did not exceed the level of concern. The risk to freshwater algae from acute exposure to mandestrobin and S-2200 *R*-isomer was thus further assessed (see Section 4.2.3).

**Marine/estuarine invertebrates:** Mandestrobin was acutely toxic to the mysid shrimp and moderately toxic to the eastern oyster. Exposure to mandestrobin for 36 days affected the first generation growth and survival of the mysid shrimp. Mandestrobin had no chronic effects on the sediment dwelling estuarine amphipod.

The risk quotient for marine invertebrates (mysid shrimp) resulting from acute and chronic exposure to mandestrobin exceeded the level of concern at screening level. The risk to marine invertebrates was, thus, further assessed (see Section 4.2.3).

**Marine/estuarine fish:** Acute exposure to mandestrobin had no adverse effects to the sheepshead minnow at the highest test concentration. Exposure to mandestrobin during early life stages of sheepshead minnows resulted in significant reductions in total length, wet weight and dry weight.

The screening level risk quotient for marine fish resulting from acute exposure to mandestrobin exceeded the level of concern. The risk quotients for marine fish resulting from chronic exposure to mandestrobin did not exceed the level of concern at the screening level. The acute risk to marine fish was, thus, further assessed (see Section 4.2.3).

**Marine/estuarine algae:** Mandestrobin exhibited acute adverse effects on cell density, growth rate and yield of the marine diatom.

The risk quotient for marine diatom resulting from acute exposure to mandestrobin did not exceed the level of concern at the screening level.

### 4.2.3 Further characterization of risk to aquatic organisms

#### 4.2.3.1 Assessment of potential risk from spray drift

To further characterize the risk to fish, amphibians, crustaceans and algae, refined EECs for aerial application were calculated using a maximum drift deposition percent at one metre downwind from the point of application. The maximum percent drift deposition for aerial and ground application and an ASAE 'coarse' droplet size (as specified on the product labels) is 17% and 3% of the application rate, respectively. The EECs were calculated for water bodies 15-cm and 80-cm deep.

The refined risk quotients for fish, crustacean (mysid shrimp) and marine diatom indicate that the level of concern from exposure to mandestrobin, S-2200 *R*-isomer and S-2200-ORC due to spray drift is not exceeded. The refined risk quotients for amphibians and freshwater algae indicate that the level of concern from mandestrobin exposure due to spray drift is exceeded for aerial application, but not exceeded for ground application. It was determined that drift mitigation measures in the form of spray buffer zones were necessary.

#### 4.2.3.2 Assessment of potential risk from run-off

The risk from exposure to run-off into a body of water directly adjacent to the application field was determined using the run-off 90th percentile of the EECs predicted by PRZM-EXAMS. The risk quotients for exposure to mandestrobin, S-2200 *R*-isomer and the transformation product S-2200-ORC were calculated using toxicity endpoints and EECs representing the 90th percentile of 96-hour concentration.

The risk quotients for aquatic organisms resulting from exposure to S-2200 *R*-isomer and S-2200-ORC through runoff do not exceed the level of concern. However, the risk quotients from exposure of mandestrobin to amphibians, freshwater algae and marine crustaceans through runoff marginally exceeded the level of concern (RQ ≤ 2.5). Standard precautionary label statements are required on the product label to inform users of best practices to minimize potential run-off from treated fields.

## 5.0 Value

### 5.1 Consideration of Benefits

Registration of mandestrobin, and the end-use products that contain this new active ingredient, will provide Canadian growers and turf managers with additional products on the market with which to address major disease problems.

A number of fungicides, including some from the same mode of action group, are registered on the subject crops to control or suppress the plant diseases indicated on the mandestrobin product labels. Refer to Appendix I, Table 22 for further information on the currently available alternatives grouped according to their modes of action.

With broad-ranging efficacy and two methods of application, mandestrobin represents a valuable addition to an effective integrated pest management approach for various cropping systems. As multiple alternative fungicides from different mode of action groups are currently registered for most diseases appearing on the foliar product and seed treatment labels, appropriate resistance management strategies can be implemented. The use patterns being registered for mandestrobin will allow application of this active ingredient in combination with good agricultural practices, including cultural methods that help to lower disease pressure.

### 5.2 Effectiveness Against Pests

**S-2200 4 SC Fungicide; S-2200 4 SC AG Fungicide; S-2200 4 VPP Fungicide (foliar products)**

Efficacy data from a total of 33 small scale trials conducted between 2006 and 2012 were reviewed to support the value of nine different disease claims on the foliar-applied mandestrobin products. A complete list of supported uses with additional details is provided in Appendix I, Table 23. Most trials were located either in Canada or northern United States. Depending on the crop disease combinations, the levels of efficacy demonstrated across the different trials were consistent with performance standards expected from claims of either control or suppression. In addition, low water spray volumes were used for ground applications in six of the trials provided with the intention of simulating aerial applications. No reduction in efficacy was observed from these treatments, thereby supporting directions for aerial applications on canola.

**S-2200 3.2 FS Fungicide (seed treatment product)**

Twenty small scale field and greenhouse efficacy trials, conducted in Canada between 2011 and 2013, were reviewed in support of the claims on the mandestrobin-containing seed treatment product S-2200 3.2 FS Fungicide. Evidence of efficacy from four bioassays was also considered in support of the product's label. Mandestrobin was demonstrated to be effective in reducing the severity and incidence of seed decay and seedling diseases caused by various seed- and soil-borne pathogens, including *Fusarium* and *Rhizoctonia*. In the majority of tested crop/pathogen combinations, mandestrobin was effective in controlling the diseases in question. However, when assessing seed decay caused by the pathogen *Phomopsis* in soybean, mandestrobin seed treatments resulted in disease suppression rather than control.

### 5.3 Non-Safety Adverse Effects

Phytotoxicity resulting from applications of mandestrobin-containing products was not reported in any of the available trial data. There is no indication that non-safety adverse effects would result from S-2200 4 SC Fungicide, S-2200 4 SC AG Fungicide, S-2200 4 SC VPP Fungicide or S-2200 3.2 FS Fungicide when applied to crops in accordance with label directions and restrictions.

### 5.4 Supported Uses

A complete list of supported uses is provided in Appendix I, Table 22.

## 6.0 Pest Control Product Policy Considerations

### 6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, in other words, persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, mandestrobin and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[9] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Mandestrobin does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Appendix I, Table 21 for comparison with Track 1 criteria.

---

[9] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

- Mandestrobin does not form any transformation products that meet all Track 1 criteria. Major transformation products S-2200-OR, S-2200-ORC and S-2200-PR are formed only by aqueous phototransformation. They are not expected to be formed in important quantities in the environment as aqueous phototransformation is restricted to the upper layer of clear water bodies.

### 6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02,[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusion:

- Technical grade mandestrobin (S-2200 Fungicide Technical) and the end-use products S-2200 4 SC Fungicide, S-2200 3.2 FS Fungicide, S-2200 4 SC Ag Fungicide and S-2200 4 SC VPP Fungicide do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

  The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

## 7.0 Summary

### 7.1 Human Health and Safety

The toxicology database submitted for mandestrobin is adequate to define the majority of toxic effects that may result from exposure. The main targets were the liver (mice, rats, dogs), thyroid gland (rats) and kidneys (mice, rats) in several short- and long-term studies. There was evidence of increased susceptibility of the young in the toxicity studies submitted, but the level of concern was low. There was equivocal evidence of oncogenicity in rats following longer-term dosing. The risk assessment protects against the toxic effects noted by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

---

[6] *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

[7] NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* under the *New Pest Control Products Act.*

[8] DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

Mixers, loaders, and applicators handling S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, S-2200 4 SC VPP Fungicide, and S-2200 3.2 FS Fungicide, and workers re-entering treated areas of rapeseed, climbing vine fruit, low-growing berries, turfgrass and sod, and planting treated corn, legumes, and rapeseed seeds are not expected to be exposed to levels of mandestrobin that will result in an unacceptable risk when these products are used according to label directions. The personal protective equipment and restricted entry interval on the product labels are adequate to protect workers. The S-2200 3.2 FS Fungicide label also includes the requirement to treat seeds in commercial facilities using closed mix, load, and transfer seed treating equipment.

Residential exposures to individuals contacting treated turf, including golfing, are not expected to result in risks of concern when S-2200 4 SC VPP Fungicide is used according to label directions. Exposure to the public entering pick-your-own strawberry and lowbush blueberry farms, following treatment with S-2200 4 SC Ag Fungicide, is also not expected to result in risks of concern.

The nature of the residues in plants is adequately understood. The residue definition for enforcement and risk assessment is mandestrobin in plant matrices. The proposed use of mandestrobin on rapeseed (canola), corn, grapes, strawberries, and soybeans does not constitute a risk of concern from chronic dietary exposure (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs. The PMRA recommends that the following MRLs be specified for residues of mandestrobin.

| Commodity | Recommended MRL (ppm) |
|---|---|
| Raisins | 7.0 |
| Small fruit vine climbing (Crop Subgroup 13-07F, except fuzzy kiwifruit) | 5.0 |
| Low growing berry (Crop Subgroup 13-07G, except cranberry) | 3.0 |
| Rapeseed (Crop Subgroup 20A) | 0.5 |
| Legume vegetables (Crop Group 6, except cowpea and field pea), corn (field, popcorn, sweet) | 0.02 |

## 7.2 Environmental Risk

To mitigate risks to non-target organisms, spray buffer zones to protect sensitive aquatic and terrestrial habitats from spray drift and label statements to inform users of potential risks to the environment are required. With these measures in place, risks to the environment from the use of mandestrobin are considered to be acceptable.

### 7.3 Value

The value information submitted was sufficient to support the registration of 16 fungal disease claims for four new end-use products containing the new fungicidal active ingredient mandestrobin. Intended either for foliar applications or seed treatments, the supported uses cover a broad range of diseases in economically important field and horticultural crops including turfgrass. Registration of these products will provide Canadian growers and producers additional disease management products with a new active ingredient from a mode of action group with a well-established efficacy profile.

## 8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Mandestrobin Technical (previously known as S-2200 Fungicide Technical) and the associated end-use products: S-2200 4 SC Fungicide, Intuity Fungicide (previously known as S-2200 4 SC Ag Fungicide), Pinpoint Fungicide (previously known as S-2200 4 SC VPP Fungicide), and S-2200 3.2 FS Fungicide, containing the technical grade active ingredient mandestrobin, for the management of various fungal diseases in canola and other oilseed crops, corn, grape, legume vegetables, strawberry and other low growing berries, as well as turfgrass.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

## List of Abbreviations

| | |
|---|---|
| ℃ | degrees Celsius |
| ♀ | female |
| ♂ | male |
| ↑ | increasing |
| ↓ | decreasing |
| ε | emittance |
| λ | wavelength |
| µg | microgram(s) |
| µM | micromolar(s) |
| 1/n | exponent for the Freundlich isotherm |
| a.i. | active ingredient |
| abs | absolute |
| AD | administered dose |
| ADI | acceptable daily intake |
| ADME | absorption, distribution, metabolism and excretion |
| AHETF | Agricultural Handlers Exposure Task Force |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| APTT | activated partial thromboplastin time |
| appl. | application |
| AR | applied radioactivity |
| ARfD | acute reference dose |
| ARTF | Agricultural Re-entry Task Force |
| ASAE | American Society of Agricultural Engineers |
| atm | atmosphere |
| ATPD | area treated per day |
| BAF | bioaccumulation factor |
| BBCH | Biologishe Bundesanstalt, Bundessortenamt and Chemical industry |
| BCF | bioconcentration factor |
| bw | body weight |
| bwg | body weight gain |
| Bz | benzyl |
| $C_{max}$ | maximum plasma concentration |
| CAF | composite assessment factor |
| CAS | Chemical Abstracts Service |
| CDC | Center for Disease Control |
| CDN | Canadian |
| CEPA | *Canadian Environmental Protection Act* |
| CG | Crop Group |
| CHL | chinese hamster lung cell line |
| cm | centimetre(s) |
| $cm^2$ | centimetre(s) squared |
| $CO_2$ | carbon dioxide |
| conj. | conjugated |
| CSG | Crop Sub-Group |

| | |
|---|---|
| CYP | cytochrome P450 |
| d | day(s) |
| DALA | days after last application |
| DAT | days after treatment |
| DEEM-FCID | Dietary Exposure Evaluation Model – Food Commodity Intake Database |
| DFOP | double first-order in parallel |
| DFR | dislodgeable foliar residue |
| DIR | Directive |
| DNA | deoxyribonucleic acid |
| $DT_{50}$ | dissipation time 50% (the dose required to observe a 50% decline in concentration) |
| $DT_{90}$ | dissipation time 90% (the dose required to observe a 90% decline in concentration) |
| dw | dry weight |
| $E_bC_{50}$ | $EC_{50}$ in terms of algal biomass |
| $EC_{25}$ | effective concentration on 25% of the population |
| $EC_{50}$ | effective concentration on 50% of the population |
| *E. coli* | *Escherichia coli* |
| EDE | estimated daily exposure |
| EEC | estimated environmental concentration |
| $ER_{25}$ | effective rate on 25% of the population |
| $ER_{50}$ | effective rate on 50% of the population |
| $F_1$ | first generation |
| $F_2$ | second generation |
| fc | food consumption |
| FDA | *Food and Drugs Act* |
| FIR | food ingestion rate |
| FRAC | Fungicide Resistance Action Committee |
| FS | flowable suspension |
| g | gram(s) |
| GAP | Good Agricultural Practice |
| GC-MS | gas chromatography with mass spectrometry |
| GI | gastrointestinal |
| GUS | groundwater ubiquity score |
| h | hour(s) |
| H295R | human adrenocarcinoma cell line |
| ha | hectare(s) |
| HAFT | highest average field trial value |
| hAR | human androgen receptor |
| HCl | hydrochloric acid |
| HeLa | Henrietta Lacks |
| hERa | human oestrogen receptor alpha |
| HDPE | High-density polyethylene |
| HPLC | high performance liquid chromatography |
| HPLC-MS/MS | high performance liquid chromatography with tandem mass spectrometry |
| HPRT | hypoxanthine phosphorybosyl transferase |
| ID | identification |

| | |
|---|---|
| ILV | independent laboratory validation |
| IORE | indeterminate order rate equation |
| IUPAC | International Union of Pure and Applied Chemistry |
| K+CWHR | kernels and cobs with husk removed |
| kg | kilogram(s) |
| $K_d$ | soil-water partition coefficient |
| $K_F$ | Freundlich adsorption coefficient |
| $K_{FOC}$ | Freundlich adsorption coefficient normalized to organic carbon |
| $K_{oc}$ | organic-carbon partition coefficient |
| $K_{ow}$ | *n*–octanol-water partition coefficient |
| L | litre(s) |
| LAFT | lowest average field trial value |
| $LC_{50}$ | lethal concentration 50% |
| LC-MS/MS | liquid chromatography with tandem mass spectrometry |
| $LD_{50}$ | lethal dose 50% |
| LLNA | local lymph node assay |
| LOAEL | lowest observed adverse effect level |
| LOC | level of concern |
| LOQ | limit of quantitation |
| $LR_{50}$ | lethal rate 50% |
| LSC | liquid scintillation counting |
| $m^2$ | square metre(s) |
| $m^3$ | cubed metre(s) |
| Max. | maximum |
| mg | milligram(s) |
| Min. | minimum |
| mL | millilitre(s) |
| M/L/A | mixer/loader/applicator |
| MAS | maximum average score |
| MIS | maximum irritation score |
| MOA | mode of action |
| MOE | margin of exposure |
| mol | mole |
| MQL | minimum quantification limit |
| MRL | maximum residue limit |
| m/z | mass-to-charge ratio of an ion |
| n | number of field trials |
| N/A or n/a | not applicable |
| NAFTA | North American Free Trade Agreement |
| NaOH | sodium hydroxide |
| NC | not classified |
| NCHS | National Center for Health Statistics |
| NHANES/ WWEIA | National Health and Nutritional Examination Survey, What We Eat in America |
| nm | nanometre(s) |
| NOAEL | no observed adverse effect level |
| NOEC | no observed effect concentration |

| | |
|---|---|
| NOEL | no observed effect level |
| NZW | New Zealand white |
| OC | organic carbon content |
| ORETF | Outdoor Residential Exposure Task Force |
| Pa | Pascal |
| PBI | plantback interval |
| PES | post-extraction solids |
| Ph | phenoxy |
| PHED | Pesticide Handlers Exposure Database |
| PHI | preharvest interval |
| p*K*a | dissociation constant |
| PLT | platelet |
| PMRA | Pest Management Regulatory Agency |
| PND | postnatal day |
| ppb | parts per billion |
| PPE | personal protective equipment |
| ppm | parts per million |
| PT | prothrombin time |
| PYO | pick your own |
| RAC | raw agricultural commodity |
| REI | restricted entry interval |
| rel | relative |
| RQ | risk quotient |
| R/S | enantiomeric ratio |
| SC | soluble concentrate |
| SD | standard deviation |
| SEEDTROPEX | Seed Treatment Operator Exposure Task Force |
| SFO | single first order |
| SOP | Standard Operating Procedure |
| SPN | Science Policy Notice |
| *S. typhimurium* | *Salmonella typhimurium* |
| $t_{1/2}$ | total elimination half-life |
| T3 | tri-iodothyronine |
| T4 | thyroxine |
| TLC | thin layer chromatography |
| $t_{max}$ | time to reach maximum plasma concentration |
| TG | technical grade |
| $t_{R\ IORE}$ | representative half-life dissipation in soil calculated with the IORE model |
| TRR | total radioactive residue |
| TRT. | treatment |
| TSH | thyroid-stimulating hormone |
| TSMP | Toxic Substances Management Policy |
| TTR | turf transferable residue |
| UDP | uridine 5'-diphospho- |
| UF | uncertainty factor |
| UGT | UDP-glucuronosyltransfase |
| UR | unextracted residues |

| | |
|---|---|
| US | United States |
| USEPA | United States Environmental Protection Agency |
| UV | ultraviolet |
| vs. | verses |
| v/v | volume per volume dilution |
| v/v/v | volume per volume per volume dilution |
| w | week(s) |
| wt(s) | weight(s) |

# Appendix I Tables and Figures

## Table 1a Residue Analysis for Environmental Media

| Matrix | Method ID | Analyte | Method Type | LOQ | Reference |
|---|---|---|---|---|---|
| Soil | CLE 8211772-01V | S-2200 R isomer | LC-MS/MS *m/z* 314→192 | 0.0025 mg/kg | 2377924 |
| | | S-2200 S isomer | *m/z* 314→192 | | |
| | | De-Xy-S-2200 | *m/z* 210→192 | 0.005 mg/kg | |
| | | 2-COOH-S-2200 | *m/z* 344→192 | | |
| | | 5-COOH-S-2200 | *m/z* 344→160 | | |
| Soil | RM-48S-3 | S-2200 | HPLC-MS/MS *m/z* 314→192 | 0.02 mg/kg | 2377938 and 2377849 |
| | | DX-CA-S-2200 | *m/z* 224→146 | | |
| | | 2-COOH-S-2200 | *m/z* 344→192 | | |
| | | 5-COOH-S-2200 | *m/z* 344→192 | | |
| | | 2-CONH2-S-2200 | *m/z* 343→192 | | |
| | | 5-CONH2-S-2200 | *m/z* 343→192 | | |
| Water | Not stated | S-2200 | HPLC-MS/MS *m/z* 314→192 | 0.10 µg/L | 2377854 and 2377857 |

## Table 1b Residue Analysis for Crops

| Matrix | Method ID | Analyte | Method Type | LOQ (ppm) | Reference |
|---|---|---|---|---|---|
| Rapeseed<br>Rotational Crops: Wheat (forage, grain, straw), Lettuce, Beet (roots, leaves) | RM-48C-2A (precedent RM-48C-2) (Enforcement Method-Plant Commodities) | S-2200 | LC-MS/MS | 0.02 | 2377885 |
| Rapeseed | RM-48C-2A (ILV of enforcement method – plant) | S-2200 | LC-MS/MS | 0.02 | 2377899 |
| Only one transition was monitored for S-2200: *m/z* 314/92; however DFG-S19 method can be used as a confirmatory method for the analysis of S-2200. | | | | | |
| Rapeseed (seeds) | DFG-S19 (Multiresidue method) | S-2200 | LC-MS/MS | 0.005: *R* and *S*-isomer | 2377889 |
| Barley (grain, straw), lettuce | DFG-S19 (Validation of multiresidue method) | S-2200 | LC-MS/MS | 0.005: *R* and *S*-isomer | 2377892 |
| Radiovalidation (plant commodities) | Similar solvents were used for the metabolism studies (acetone/water; 80:20) and the enforcement method (acetone/water; 70:30). In general, extraction efficiencies were similar for both extraction methods (Tissumizer or shaking) with both solvent systems in rapeseed forage (80.3-90.9% of the TRR). Seed samples were also extracted with a Tissumizer and a solvent solution of acetone:water, 70:30, v/v, which yielded an average extraction efficiency of 108.1% of the TRR. | | | | 2377887 |
| Rapeseed, Corn (Forage and Stover) | RM-48C-1 (Data-Gathering Method – Plant | S-2200 | GC-MS | 0.02 | 2377926;<br>2377153;<br>2377152 |

| Matrix | Method ID | Analyte | Method Type | LOQ (ppm) | Reference |
|---|---|---|---|---|---|
| Corn (Grain and K+CWHR), Soybean | Commodities) | | | 0.01 | |
| Strawberry, Grape | RM-49G (Data Gathering Method – Plant Commodities) | S-2200 | LC-MS/MS | 0.02 | 2377617,<br>2377618,<br>2377620,<br>2377613 |
| Poultry muscle | RM-49M-1 (ILV of Proposed Enforcement Method – Livestock Commodities) | S-2200 | LC-MS/MS | 0.02 | 2377659 |
| If livestock feed items increase the dietary burden in cattle and poultry, a validated enforcement method using cattle fat, meat and meat byproducts, milk, and eggs will be necessary, including ILV and radiovalidation. | | | | | |

For further use expansions involving cereal grains (wheat), the applicant is requested to also measure for the metabolite De-Xy-S-2200 in the crop field trials (along with mandestrobin) as it was a major metabolite found in the metabolism studies for wheat grain and straw. The residue definition of mandestrobin may be revised as a result.

## Table 2 Chemical Names of Isomers and Metabolites of Mandestrobin

| Code/Trivial name | Chemical name |
|---|---|
| S-2167 (R-isomer of mandestrobin) | (R)-2-methoxy-N-methyl-2-[α-(2,5-xylyloxy)-o-tolyl]acetamide |
| S-2354 (S-isomer of mandestrobin) | (S)-2-methoxy-N-methyl-2-[α-(2,5-xylyloxy)-o-tolyl] acetamide |
| 2-CH$_2$OH-S-2200 | (2RS)-2-[2-(2-hydroxymethyl-5-methylphenoxymethyl)phenyl]-2-methoxy-N-methylacetamide |
| 2-COOH-S-2200 | 2-({2-[(1RS)-1-methoxy-2-(methylamino)-2-oxoethyl]benzyl}oxy)-4-methylbenzoic acid |
| 4-OH-S-2200 | (2RS)-2-[2-(4-hydroxy-2,5-dimethylphenoxymethyl)phenyl]-2-methoxy-N-methylacetamide |
| 5-COOH-S-2200 | 5-({2-[(1RS)-1-methoxy-2-(methylamino)-2-oxoethyl]benzyl}oxy)-4-methylbenzoic acid |
| De-XY-S-2200 | (2RS)-2-(2-hydroxymethylphenyl)-2-methoxy-N-methylacetamid |

## Table 3 Toxicity Profile of S-2200 3.2 FS Fungicide

**(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)**

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| Acute Oral Toxicity<br>Sprague-Dawley Rat<br>PMRA # 2378126 | LD$_{50(F)}$ = 3129 mg/kg bw<br>Low Toxicity |
| Acute Dermal Toxicity<br>Sprague-Dawley Rat<br>PMRA # 2378127 | LD$_{50(M/F)}$ > 5000 mg/kg bw<br>Low Toxicity |

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| Acute Inhalation<br>(nose-only)<br>Sprague-Dawley Rat<br>PMRA # 2378128 | $LC_{50(F)}$ > 2.08 mg/L<br>Low Toxicity |
| Eye Irritation<br>NZW rabbit<br>PMRA # 2378129 | MIS= 6.0/110<br>MAS (24, 48, 72 hour)= 0.22/110<br>Minimally irritating |
| Dermal Irritation<br>NZW Rabbit<br>PMRA # 2378130 | MIS= 1/8<br>MAS (24, 48, 72 hour)= 0/8<br>Non-irritating |
| Local Lymph Node Assay (LLNA)<br>CBA/J Mouse<br>PMRA # 2378131 | Non-sensitizer |

**Table 4** **Toxicity Profile of S-2200 4 SC Fungicide, S-2200 4 SC AG Fungicide and S-2200 4 SC VPP Fungicide**

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| Acute Oral Toxicity<br>Sprague-Dawley Rat<br>PMRA # 2377860 | $LD_{50(F)}$ = 5129 mg/kg bw<br>Low Toxicity |
| Acute Dermal Toxicity<br>Sprague-Dawley Rat<br>PMRA # 2377862 | $LD_{50(F)}$ > 5000 mg/kg bw<br>Low Toxicity |
| Acute Inhalation<br>(nose-only)<br>Sprague-Dawley Rat<br>PMRA # 2377865 | $LC_{50(F)}$ > 2.08 mg/L<br>Low Toxicity |

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| Eye Irritation<br>NZW rabbit<br>PMRA # 2377866 | MIS= 1.33/110<br>MAS (24, 48, 72 hours)= 0.33/110<br>Minimally irritating |
| Dermal Irritation<br>NZW Rabbit<br>PMRA # 2377868 | MIS= 0/8<br>MAS (24, 48, 72 hours)= 0/8<br>Non-irritating |
| Local Lymph Node Assay (LLNA)<br>CBA/J Mouse<br>PMRA # 2377870 | Non-sensitizer |

**Table 5 Toxicity Profile of Technical Mandestrobin**

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted) Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| ADME<br>(single administration [S-2200TG, S-2167, S-2358], multiple administration [S-2200TG])<br>Wistar Rat<br>PMRA #2377000, 2377089, 2377087 | Mandestrobin (benzyl-$^{14}$C-S-2200TG and phenoxy-$^{14}$C-S-2200TG; racemic mixtures), R-isomer (benzyl-$^{14}$C-S-2167), S-isomer (benzyl-$^{14}$C-S-2358). All forms of mandestrobin were rapidly absorbed (≥ 55% administered single dose (AD); 73-81% by 78 hours). Systemic exposure was proportionally higher at the low dose than at the high dose, indicating saturation of oral absorption at high dose. Peak plasma levels ($C_{max}$) were reached by 1.2-2.0 hours ($t_{max}$) after an oral dose of 5 mg/kg, and 7.0-9.1 hours after a dose of 1000 mg/kg.<br>The labeled compound was widely distributed throughout tissues, but was detected primarily in the GI tract, liver and kidney. Pancreas, uterus and ovaries also had higher levels than most other tissues. Isomers had similar tissue distribution except the S-isomer was more prevalent in GI tract than the R-isomer. There was no sex difference in distribution into tissues, except during the multiple dosing period, females kept a larger portion of the dose in the cecum/large intestine/intestinal contents, and reached peak levels in tissues outside the GI tract later than males.<br>There was no evidence of long-term accumulation of S-2200TG or its metabolites in tissues. Clearance of a single dose of S-2200TG from plasma was almost complete by 120 hours post-dose ($t_{1/2}$ = 19-23 hours at the low dose; $t_{1/2}$ = 25-29 hours at the high dose). Clearance of the S-isomer was less rapid than the R-isomer. In the repeated dose study, 85-89% of the AD was excreted by 10 days after last dose. Bile cannulated rats excreted S-2200TG faster than non-cannulated rats (97-99% vs. 40-51% of a single dose by 24 hours), suggesting enterohepatic recirculation. Excretion was consistent with all S-2200TG treatments. Fecal excretion (60-75% of AD) via bile was the primary excretion route, and renal excretion (15-21% of AD) was also important. Excretion in expired air was negligible.<br>S-2200TG is almost completely metabolized in rats via (1) oxidation followed by glucuronidation, (2) demethylation followed by oxidation, or (3) oxidation followed by demethylation. The molecule core remains essentially intact, with no cleavage of benzyl and phenoxy rings. The major metabolites excreted are: 5-CA-S-2200-NHM and 4-OH-S-2200 in feces; 4-OH-S-2200-GlucA in bile; and 5-CA-S-2200-NHM in urine. The same metabolites were identified for both isomers however at different proportions. In order of magnitude, R-isomer produced mostly 5-CA-S-2200-NHM, 5-CA-MCBX-NDM, 5-CA-2-HM-S-2200-NHM |

| | |
|---|---|
| | and 5-CA-S-2200-NDM; while S-isomer produced mostly 4-OH-S-2200 and 5-COOH-S-2200.<br>In the multiple dose study, fecal metabolites found at slightly higher levels in male than females were 5-CA-S-2200-NHM, 5-COOH-S-2200, 5-CA-2-HM-S-2200-NHM, 5-CA-2-HM-MCBX and 5-CA-MCBX-NDM.<br>Results from cannulated rats suggest that 4-OH-S-2200 and its A glucuronide (GlucA) undergo enterohepatic circulation. |
| Acute Oral Toxicity<br>Wistar Rat<br>PMRA # 2177929 | $LD_{50♀}$ > 2000 mg/kg bw<br>Low Toxicity |
| Acute Dermal Toxicity<br>Wistar Rat<br>PMRA # 2177936 | $LD_{50♂/♀}$ > 2000 mg/kg bw<br>Low Toxicity |
| Acute Inhalation (nose-only)<br>Wistar Rat<br>PMRA # 2177937 | $LC_{50♂/♀}$ > 4.56 mg/L<br>Low Toxicity |
| Eye Irritation<br>NZW rabbit<br>PMRA # 2177939 | MIS= 10.3/110<br>MAS (24, 48, 72 hour)= 4.0/110<br>Minimally irritating |
| Dermal Irritation<br>NZW Rabbit<br>PMRA # 2177940 | MIS= 0/8<br>MAS (24, 48, 72 hour)= 0/8<br>Non-irritating |
| Sensitization Study (Maximization Test)<br>Guinea Pig<br>PMRA # 2177941 | Non-sensitizer |
| 28-Day dermal toxicity<br>Wistar Rat<br>PMRA # 2177957 | NOAEL = 1000 mg/kg bw/day<br>LOAEL was not determined due to absence of effects up to the limit dose. |
| 90-Day oral toxicity (diet)<br>CD-1 Mouse<br>PMRA # 2177946 | NOAEL= 807/529 mg/kg bw/day in ♂/♀<br>LOAEL was not determined in ♂<br>LOAEL ♀ = 1111 mg/kg bw/day; effects included decreased bw and lower bwg |
| 90-Day oral toxicity (diet)<br>Wistar Rat<br>PMRA # 2177948 | NOAEL= 283/320 mg/kg in ♂/♀<br>LOAEL= 743/789 mg/kg bw/day in ♂/♀; effects included ↑ incidence hepatocyte hypertrophy and severity, ↑ total cholesterol, ↑ incidence of thyroid follicular cell hypertrophy; ↑ liver wts, ↑ incidence large liver, ↑ incidence liver agonal congestion/ hemorrhage, ↑ severity thyroid follicular hypertrophy (♂); ↑ rel liver wt (♀) |
| 90-Day oral toxicity (diet)<br>Beagle Dog | NOAEL= 91/103 mg/kg bw/day in ♂/♀<br>LOAEL= 268/304 mg/kg bw/day in ♂/♀; effects included ↑ incidence liver centrilobular degeneration and severity, ↑ incidence dark liver; ↑ incidence large liver (♂) ; ↑ ALP (♀) |

| | |
|---|---|
| PMRA # 2377954 | |
| 1-Year oral toxicity (diet)<br>Beagle Dog<br>PMRA # 2377952 | NOAEL= 92 mg/kg bw/day<br>LOAEL= 181/226 mg/kg bw/day in ♂/♀; effects included ↓ bw, ↑ liver wt, ↑ incidence liver centrilobular degeneration, agonal congestion/hemorrhage, hepatocyte hypertrophy and severity, hepatocyte pigment, ↑ ALP, ↑ ALT, ↑ PLT; ↓ bwg (♂); ↓ PT and APTT, thin appearance and reduced muscle tone (1/4) (♀) |
| 78- week Oncogenicity (diet)<br>CD-1 Mouse<br>PMRA #2377960 | NOAEL = 239/994 mg/kg bw/day in ♂/♀<br>LOAEL not determined in ♀<br>LOAEL = 824 mg/kg bw/day in ♂; effects included ↑ incidence of corticomedullary mineralization (♂)<br>No evidence of oncogenicity |
| 2-Year combined oral chronic toxicity /carcinogenicity (diet)<br>Wistar rat<br>PMRA # 2377961 | NOAEL = 130/27 mg/kg bw/day in ♂/♀<br>LOAEL = 449/135 mg/kg bw/day in ♂/♀; effects included ↑ liver wt, liver hypertrophy, thyroid follicular cell hypertrophy (♂); ↓ bw, ↓ bwg, rel liver wt, hepatocyte hypertrophy, ↑ incidence of corticomedullary mineralization (♀)<br>Equivocal evidence of oncogenicity based on a treatment-related increase in ovary sex cord-stromal benign tumors in female rats (2, 0, 1, 4, 6). |
| 2-generation reproductive toxicity study<br>BrlHan:WIST@Jcl (GALAS) Rats<br>PMRA # 2377964 | NOAEL (parental) = 1000 ppm (56/63 mg/kg bw/day in ♂/♀)<br>LOAEL (parental) = 3000 ppm (166/195 mg/kg bw/day in ♂/♀); effects included ↑ bile duct brown pigmentation and periductular inflammatory cell infiltration (with liver weight and hypertrophy at the same dose)<br>NOAEL (offspring) = 3000 ppm (195 mg/kg bw/day)<br>LOAEL (offspring) = 10000 ppm (628 mg/kg bw/day); effects included ↓ bw F1/F2 from PND 7<br>NOAEL (reproductive) = 10000 ppm (629 mg/kg bw/day)<br>LOAEL (reproductive) ≥ 10000 ppm (629 mg/kg bw/day)<br>No evidence of sensitivity of the young |
| Developmental Toxicity Study in Rats<br>Crl:WI(Han) Rats<br>PMRA # 2377967 | Maternal NOAEL = 1000 mg/kg bw/day<br>Maternal LOAEL > 1000 mg/kg bw/day<br>Developmental NOAEL = 300 mg/kg bw/day<br>Developmental LOAEL = 1000 mg/kg bw/day; effects included ↑ increased incidences of litters containing foetuses with distended ureter or delayed skull ossification<br>Evidence of sensitivity of the young |
| Developmental Toxicity Study in Rabbits<br>Hsd:IfNZW Rabbits<br>PMRA # 2377970 | Maternal NOAEL = 1000 mg/kg bw/day<br>Maternal LOAEL > 1000 mg/kg bw/day<br>Developmental NOAEL = 1000 mg/kg bw/day<br>Developmental LOAEL > 1000 mg/kg bw/day<br>No evidence of sensitivity of the young |
| Bacterial Reverse Mutation Assay (Ames test)<br>PMRA # 2377971 | Negative in *S. typhimurium* strains (TA 98, TA100, TA1535, TA1537 and TA1538) and *E. coli* WP2uvrA in the presence and absence of metabolic activation. |
| *In vitro* Mammalian Cell Assay (forward gene mutation)<br>PMRA#2377978 | Negative in V79-HPRT cells |

| | |
|---|---|
| *In vitro* Mammalian Clastogenicity Assay (chromosomal aberration)<br>PMRA#2377984 | Negative in Chinese hamster lung cells (CHL/IU) |
| Micronucleus Assay<br>PMRA #2377985 | Negative in BDF$_1$[SPF] mice<br>No mortality, clinical signs of toxicity and no differences in body weight compared to controls. |
| Acute neurotoxicity (gavage)<br>Wistar Rat<br>PMRA # 2377992 | NOAEL = 1000 mg/kg bw in ♂/♀<br>LOAEL = 2000 mg/kg bw in ♂/♀; effects included ↓ overall locomotor activity (total and/or ambulatory counts) on study day 0 (0-30 min) |
| 90-Day neurotoxicity study<br>Wistar rat<br>PMRA # 2377994 | NOAEL = 338/1223 mg/kg bw/day in ♂/♀<br>LOAEL not determined in ♀<br>LOAEL = 1024 mg/kg bw/day in ♂; effects included ↓ bw and lower bwg, ↓ fc (♂)<br>No evidence of neurotoxicity |
| 28-Day Immunotoxicity (diet)<br>Wistar rat<br>PMRA # 2378005 | NOAEL = 471 mg/kg bw/day in ♀<br>LOAEL = 1419 mg/kg bw/day in ♀; effects included ↑ spleen wt (♀) |
| Special study<br>Ovary: Reporter Genes Assay (hERα and hAR assays)<br>PMRA # 2378010 | Neither S-2200TG nor its metabolites (5-COOH-S-2200, 4-OH-S-2200, 5-CH$_2$OH-S-2200 and 5-CA-S-2200-NHM) showed agonistic or antagonistic effects on hERα and hAR from HeLa cells derived from human uterine cervix carcinoma.<br>Note:Test substances were assayed only once. |
| Ovary: Steroidogenesis Assay<br>PMRA # 2378006 | S-2200TG did not modulate testosterone or estradiol production under the conditions of this study up to 30 µM (viability ≥ 80%) in H295R cells. |
| Liver and thyroid changes (diet)<br>Wistar Rat<br>PMRA # 2378008 | 7-day treatment:<br>**≥23/26 mg/kg bw/day in ♂/♀:** ↑ T4-UGT (♂)<br>**≥116/131 mg/kg bw/day in ♂/♀:** ↑ CYP2B ; ↑ rel liver wt (♀)<br>**≥379/420 mg/kg bw/day in ♂/♀:** ↓ fc, diffuse hepatocellular hypertrophy, ↑ DNA synthesis ; ↓ bw, ↓ bwg, ↑ rel liver wt (♂); ↑ thyroid wt , diffuse thyroid follicular cell hypertrophy (♀)<br>**744/812 mg/kg bw/day in ♂/♀:** enlarged liver, bile duct brown pigment, peribiliary inflammation, ↓ T4 (♂) ; ↓ bw , ↓ bwg , ↑ abs liver wt, ↑ T4-UGT, ↑ TSH (♀)<br>14-day treatment:<br>**796/952 mg/kg bw/day in ♂/♀:** ↓ bwg , ↑ liver wt, ↑ thyroid wt, diffuse hepatocellular hypertrophy (♂♀) with ↑ severity versus 7-day treatment (♂), ↓ T4, ↑ TSH ; ↑ DNA synthesis (♂); ↓ bw , diffuse thyroid follicular cell hypertrophy, ↓ T3 (♀)<br>**7-day treatment + recovery:**<br>bw and bwg recoveries, fc recovery, liver wt still significantly ↑ in ♂, recovery for thyroid wt, no remarkable pathology findings at necropsy, ↑ CYP4A, recovery for thyroid hormone levels except for T4 in ♂ |

## Table 6 Toxicity Profile of Metabolites of Mandestrobin

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| Acute Oral Toxicity<br>2-CH2OH-S-2200<br>Wistar Rat<br>PMRA # 2377935 | $LD_{50♀}$ > 2000 mg/kg bw<br>Low Toxicity |
| Bacterial Reverse Mutation Assay (Ames test)<br>2-CH2OH-S-2200<br>PMRA#2377976 | Negative in *S. typhimurium* strains (TA 98, TA100, TA1535, TA1537 and TA1538) and *E. coli* WP2uvrA in the presence and absence of metabolic activation. |
| Acute Oral Toxicity<br>2-COOH-S-2200<br>Wistar Rat<br>PMRA # 2377932 | $LD_{50♀}$ > 2000 mg/kg bw<br>Low Toxicity |
| Bacterial Reverse Mutation Assay (Ames test)<br>2-COOH-S-2200<br>PMRA#2377973 | Negative in *S. typhimurium* strains (TA 98, TA100, TA1535, TA1537 and TA1538) and *E. coli* WP2uvrA in the presence and absence of metabolic activation. |
| *In vitro* Mammalian Clastogenicity Assay (chromosomal aberration)<br>2-COOH-S-2200<br>PMRA#2377983 | Positive at 2200 µg/mL after 24 hours in absence of metabolic activation (relative cell growth 48.8%) in Chinese hamster lung cells (CHL/IU). |
| Micronucleus Assay<br>2-COOH-S-2200<br>PMRA #2377986 | Negative in $BDF_1$[SPF] mice.<br>No mortality, clinical signs of toxicity and no differences in body weight compared to controls. |
| Acute Oral Toxicity<br>4-OH-S-2200<br>Wistar Rat<br>PMRA # 2377944 | $LD_{50♀}$ > 2000 mg/kg bw<br>Low Toxicity |
| Bacterial Reverse Mutation Assay (Ames test)<br>4-OH-S-2200<br>PMRA#2377977 | Negative in *S. typhimurium* strains (TA 98, TA100, TA1535, TA1537 and TA1538) and *E. coli* WP2uvrA in presence and absence of metabolic activation. |
| Acute Oral Toxicity<br>5-COOH-S-2200<br>Wistar Rat<br>PMRA # 2377933 | 300 mg/kg bw < $LD_{50♀}$ < 2000 mg/kg bw<br>High Toxicity<br>All the animals dosed at 2000 mg/kg bw died within 24 hours.<br>2000 mg/kg bw: the animals presented retention of a white fluid in the stomach, yellowish-white fluid content in the small intestine and foamy fluid in the trachea |

| | |
|---|---|
| Bacterial Reverse Mutation Assay (Ames test)<br>5-COOH-S-2200<br>PMRA#2377975 | Negative in *S. typhimurium* strains (TA 98, TA100, TA1535, TA1537 and TA1538) and *E. coli* WP2uvrA in presence or absence of metabolic activation. |
| *In vitro* Mammalian Cell Assay (forward gene mutation)<br>5-COOH-S-2200<br>PMRA#2377981 | Negative in V79-HPRT cells in presence and absence of metabolic activation. |
| *In vitro* Mammalian Clastogenicity Assay (chromosomal aberration)<br>5-COOH-S-2200<br>PMRA#2377984 | Negative in Chinese hamster lung cells (CHL/IU) in presence and absence of metabolic activation. |
| Acute Oral Toxicity<br>De-Xy-S-2200<br>Wistar Rat<br>PMRA # 2377931 | $\text{LD}_{50♀}$ > 2000 mg/kg bw<br>Low Toxicity |
| Bacterial Reverse Mutation Assay (Ames test)<br>De-XY-S-2200<br>PMRA#2377972 | Negative in *S. typhimurium* strains (TA 98, TA100, TA1535, TA1537 and TA1538) and *E. coli* WP2uvrA in presence and absence of metabolic activation. |

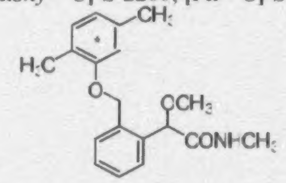
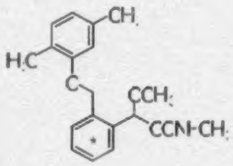
## Table 7 Toxicology Endpoints for Use in Health Risk Assessment for Mandestrobin

| Exposure Scenario | Study | Point of Departure and Endpoint | CAF$^1$ or Target MOE |
|---|---|---|---|
| Acute dietary general population | An ARfD is not required | | |
| Repeated dietary | Rat chronic toxicity/oncogenicity study | NOAEL= 27 mg/kg bw/day; effects included reduced body weight/body weight gains as well as liver and kidney effects | 100 |
| | ADI = 0.3 mg/kg bw/day | | |
| Short-term dermal | Rat 28-day dermal toxicity study | NOAEL= 1000 mg/kg bw/day<br>LOAEL was not determined due to absence of effects up to the limit dose. | 100 |
| Intermediate-term dermal | | | |
| Short-term inhalation$^2$ | Rat reproductive toxicity study | NOAEL= 56 mg/kg bw/day; effects included increased bile duct brown pigmentation and periductular inflammatory cell infiltration in F$_1$ parental generation. | 100 |
| Intermediate-term inhalation$^2$ | | | |
| Non-dietary oral ingestion (short-term) | Rat reproductive toxicity study | NOAEL= 56 mg/kg bw/day; effects included increased bile duct brown pigmentation and periductular inflammatory cell infiltration in F$_1$ parental generation. | 100 |
| Cancer | An increase in benign sex cord-stromal tumours in females in the rat oncogenicity study was considered equivocal based on the weight of evidence. The endpoints selected for the non-cancer risk assessment are protective of these equivocal findings. | | |

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational and residential assessments

[2] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

## Table 8 Integrated Food Residue Chemistry Summary

| **NATURE OF THE RESIDUE IN LETTUCE** | | | **PMRA # 2377840** | |
|---|---|---|---|---|
| **Radiolabel Position** | [Phenoxy-$^{14}$C]-S-2200; [Ph-$^{14}$C]-S-2200  | | [Benzyl-$^{14}$C]-S-2200; [Bz-$^{14}$C]-S-2200  | |
| In all studies, the *R/S* ratio of S-2200 remained approximately 1:1, indicating no *R/S* isomerization. | | | | |
| **Test Variety** | *Lactuca sativa* (Buttercrunch) | | | |
| **Test Site** | In individual pots in greenhouse | | | |
| **Formulation** | The test material was formulated as a 25% suspension concentrate (SC) with an approximate S-2200 R:S isomer ratio of 50:50 | | | |
| **Treatment/Rate** | 1 foliar application of 800 g a.i./ha at BBCH 43 followed by a 2nd application of 800 g a.i./ha at BBCH 48 for a total of 1600 g a.i./ha | | | |
| **PHI (days)** | Immature lettuce leaves: 5 days after the 1st application<br>Mature lettuce leaves: 5 days after the 2nd application | | | |
| **Analytical Method for Overall TRR Identification & Characterization** | LSC and combustion<br>HPLC and TLC co-chromatography | | | |
| **Extraction Solvents** | Acetonitrile (surface wash only); acetone/water (80:20; v/v); acetone/water/hydrochloric acid (80:20:1; v/v/v) | | | |
| **Post-Extraction Solids (PES)** | Enzymatic hydrolysis with Driselase (enzyme mixture of fungal carbohydrolases), mild acid hydrolysis (0.1M HCl, 40°C, overnight) and mild base hydrolysis (0.1M NaOH, 40°C, overnight) | | | |
| **Storage Stability** | Representative samples from both radiolabels were re-extracted and analysed to verify the stability of the analytes during freezer storage (5 months). Similar profiles were obtained, which indicated stability of [$^{14}$C]-S-2200 metabolites in lettuce samples. | | | |
| **Matrices** | **Total Rate (g a.i./ha)** | **PHI (days)** | **[Ph-$^{14}$C]-S-2200** | **[Bz-$^{14}$C]-S-2200** |
| | | | **TRR (ppm, in S-2200 equivalents)** | |
| Immature Lettuce Leaves | 800 | 5 (after 1st appl.) | 35.11 | 27.94 |
| Mature Lettuce Leaves | 1600 | 5 (after 2nd appl.) | 43.14 | 41.59 |
| **Metabolites Identified** | **Major Metabolites (>10% of the TRR)** | | | |
| **Radiolabel Position** | **[Ph-$^{14}$C]-S-2200** | | **[Bz-$^{14}$C]-S-2200** | |
| Lettuce – Immature leaves | S-2200 | | S-2200 | |
| Lettuce – Mature leaves | S-2200 | | S-2200 | |
| Most of the radioactivity was recovered in the surface washes (78.5-88.4% of the TRR). The metabolites De-Xy-S2200, MCBX, and conjugates of 2-$CH_2OH$-S-2200, 4-OH-S-2200, 5-$CH_2OH$-S-2200 and 5-COOH-S-2200 were detected along with several other minor metabolites. | | | | |

| **NATURE OF THE RESIDUE IN RAPESEED** | | **PMRA # 2377845** |
|---|---|---|
| **Radiolabel Position** | **[Ph-$^{14}$C]-S-2200** | **[Bz-$^{14}$C]-S-2200** |
| **Test Variety** | *Brassica napus* L. (Phoenix Liberty Link) | |
| **Test Site** | In individual pots maintained under open field conditions (grown to maturity) | |
| **Formulation** | The test material was formulated as a 25% suspension concentrate (SC) with an approximate S-2200 R:S isomer ratio of 50:50 | |
| **Treatment/Rate** | TRT # 1: 1 foliar application of 400 g a.i./ha at BBCH 55-61 | TRT # 2: 1 foliar application of 400 g a.i./ha at BBCH 66-67, and a 2nd application 14-days after the 1st for a total of 800 g a.i./ha/season |
| **PHI (days)** | 54 (seeds) | 14 (forage); 40 (seeds) |
| **Analytical Method for Overall TRR Identification & Characterization** | LSC and combustion<br>HPLC and TLC co-chromatography | |
| **Extraction Solvents** | Acetonitrile (forage surface wash); hexane (seed samples only); acetone/water (80:20; v/v); acetone/water/hydrochloric acid (80:20:1; v/v/v) | |
| **Post-Extraction Solids (PES)** | Sequential enzyme hydrolysis with amylase and protease followed by weak acid hydrolysis (1M HCl, 40°C, overnight), strong acid hydrolysis (6M HCl, 80°C, 4 hours), weak base hydrolysis (0.1M NaOH, 40°C, overnight) and strong base hydrolysis (6M NaOH, 80°C, overnight) | |
| **Storage Stability** | Representative samples from both radiolabels were re-extracted and analysed to verify the stability of the analytes during freezer storage (7-11 months). Similar profiles were obtained, which indicated stability of [$^{14}$C]-S-2200 metabolites in rapeseed samples. | |

| **Matrices** | **Total Rate (g a.i./ha)** | **PHI (days)/ Growth Stage** | **[Ph-$^{14}$C]-S-2200** | **[Bz-$^{14}$C]-S-2200** |
|---|---|---|---|---|
| | | | **TRR (ppm, in S-2200 equivalents)** | |
| Rapeseed – Seeds (TRT #1) | 400 | 54 (BBCH 89) | 0.05 | 0.11 |
| Rapeseed – Seeds (TRT #2) | 800 | 40 (BBCH 89) | 0.47 | 0.64 |
| Rapeseed – Forage (TRT #2) | 800 | 14 (BBCH 55-61) | 3.99 | 3.44 |

| **Metabolites Identified** | **Major Metabolites (>10% of the TRR)** | |
|---|---|---|
| **Radiolabel Position** | **[Ph-$^{14}$C]-S-2200** | **[Bz-$^{14}$C]-S-2200** |
| Rapeseed (Seeds) – TRT #1 | None | None |
| Rapeseed (Seeds) – TRT #2 | S-2200, 4-OH-S-2200 (conj.) | S-2200, 4-OH-S-2200 (conj.) |
| Rapeseed (Forage) – TRT #2 | S-2200, 2-$CH_2OH$-S-2200 (conj.), 4-OH-S-2200 (conj.) | S-2200, 2-$CH_2OH$-S-2200 (conj.), 4-OH-S-2200 (conj.) |

For forage, the radioactivity in the surface rinse ranged from 34 to 37% of the TRR, and approximately 55 to 58% of the TRR was present in the extractable fractions. For seed, approximately 81 to 99% of the TRR was present in extractable fractions from each treatment group. Minor metabolites included free forms of 5-COOH-S-2200, and MCBX and a conjugate of 5-$CH_2OH$-S-2200.

| **NATURE OF THE RESIDUE IN WHEAT** | | **PMRA # 2377842** |
|---|---|---|
| **Radiolabel Position** | **[Ph-$^{14}$C]-S-2200** | **[Bz-$^{14}$C]-S-2200** |
| **Test Variety** | *Triticum L.* (Promontory) | |
| **Test Site** | In individual pots maintained under greenhouse conditions (grown to maturity) | |
| **Formulation** | The test material was formulated as a 25% suspension concentrate (SC) with an approximate S-2200 R:S isomer ratio of 50:50 | |
| **Treatment/Rate** | A single foliar application of 300 g a.i./ha at BBCH 32 (104 days before final harvest) | |

| | |
|---|---|
| **PHI (days)** | 7 (BBCH 37 Wheat Forage); 14 (BBCH 37 Wheat Hay); 104 (BBCH 92 Wheat Grain) |
| **Analytical Method for Overall TRR<br>Identification & Characterization** | LSC and combustion<br>HPLC and TLC co-chromatography |
| **Extraction Solvents** | Acetonitrile (surface wash only); acetone/water (80:20; v/v); acetone/water/hydrochloric acid (80:20:1; v/v/v) |
| **Post-Extraction Solids (PES)** | Sequential enzyme hydrolysis with Driselase, mild acid hydrolysis (0.1M HCl, 40°C overnight) and mild base hydrolysis (0.1M NaOH, 40°C overnight) |
| **Storage Stability** | Representative samples from both radiolabels were re-extracted and analysed to verify the stability of the analytes during freezer storage (8 months). Similar profiles were obtained, which indicated stability of [$^{14}$C]-S-2200 metabolites in wheat samples |

| **Matrices** | **Total Rate (g a.i./ha)** | **PHI (days)/ Growth Stage** | **[Ph-$^{14}$C]-S-2200** | **[Bz-$^{14}$C]-S-2200** |
|---|---|---|---|---|
| | | | **TRR (ppm, in S-2200 equivalents)** | |
| Wheat Forage | 300 | 7 (BBCH 37) | 11.14 | 10.44 |
| Wheat hay | 300 | 14 (BBCH 37) | 6.21 | 9.04 |
| Wheat grain | 300 | 104 (BBCH 92) | 0.01 | 0.09 |
| Wheat straw | 300 | 104 (BBCH 92) | 1.85 | 2.49 |

| **Metabolites Identified** | **Major Metabolites (>10% of the TRR)** | |
|---|---|---|
| **Radiolabel Position** | **[Ph-$^{14}$C]-S-2200** | **[Bz-$^{14}$C]-S-2200** |
| Wheat forage | S-2200, 2-CH$_2$OH-S-2200 (conj.) | S-2200 |
| Wheat hay | S-2200, 2-CH$_2$OH-S-2200 (conj.), 4-OH-S-2200 (conj.) | S-2200, 2-CH$_2$OH-S-2200 (conj.) |
| Wheat straw | None | De-Xy-S-2200 |
| Wheat grain | None | De-Xy-S-2200 |

The radioactivity in the surface rinse ranged from 19 – 41% of the TRR for the forage and hay samples and approximately 3% TRR in the straw samples from both treatment groups. Approximately 53 - 73% of the TRR was present in the extractable fraction of the forage, hay, straw and grain from both wheat treatment groups. MCBX, 2-CH$_2$OH-S-2200 (free), 4-OH-S-2200 (free), 5-CH$_2$OH-S-2200 (free and conjugated), and 5-COOH-S-2200 (free) were considered minor metabolites. S-2200 was not detected in the wheat grain from either treatment group but the TRR was very low in these samples. De-Xy-S-2200 accounted for 2 to 12% of the TRR (0.14 - 0.33 ppm) in the forage, hay and straw samples and accounted for 61% of the TRR (0.05 ppm) in the grain sample from the [Bz-$^{14}$C]-S-2200 treatment group.

| **Nature of the Residue in Soybeans and Corn (Radiotracer)** | | **PMRA # 2378156/2378157** |
|---|---|---|
| **Test Variety** | Soybean: Pioneer 93M42; Corn: TR3026RRxTR2040RRxTR1914 | |
| **Formulation** | Formulated product as 3.2 FS: 1.20 MBq/mg applied | Formulated product as 3.2 FS: 1.21 MBq/mg applied |
| **Treatment/Rate** | [Ph-$^{14}$C]-S-2200<br>Soybean: Seed/9.33 g/100 kg<br>Corn: 11.03 g/100 kg | [Bz-$^{14}$C]-S-2200<br>Soybean: Seed/10.72 g/100 kg<br>Corn: 11.55 g/100 kg |
| **Analytical Method for Overall TRR<br>Identification & Characterization** | LSC and combustion<br>HPLC and TLC co-chromatography | |
| **Radiolabel Position** | **[Ph-$^{14}$C]-S-2200** | **[Bz-$^{14}$C]-S-2200** |
| **Matrices** | **TRR (ppm)** | **TRR (ppm)** |
| Soybean forage | 0.027, 0.038 | 0.040, 0.061 |
| Soybean hay | 0.030, 0.027 | 0.045, 0.050 |
| Soybean pod with seed | <0.005, <0.005 | <0.005, <0.005 |
| Soybean mature seed | <0.005, <0.005 | <0.005, <0.005 |
| Corn kernels plus cob | <0.005, <0.005 | <0.005, <0.005 |
| Corn forage | <0.005, <0.005 | <0.005, <0.005 |
| Corn stover | <0.005, <0.005 | 0.011, 0.005 |

| | | |
|---|---|---|
| Corn grain | <0.005, <0.005 | <0.005, <0.005 |

The total radioactive residue in treated RAC was below the minimum quantification limit (MQL) of 0.005 ppm in all RACs, with the exception of soybean (forage and hay), and corn (stover). Samples of soybean forage and hay grown from seeds treated with [Ph-$^{14}$C]-S-2200 and [Bz-$^{14}$C]-S-2200, and corn stover from seeds treated with [Bz-$^{14}$C]-S-2200 were extracted with acetonitrile in order to further characterize the residues that were detected above 5 ppb. The parent S-2200 was detected in the soybean forage, soybean hay and corn stover (<7.9% of the TRR; ≤0.003 ppm). Trace amounts of 2-COOH-S-2200 and 5-COOH-S-2200 were also observed in the soybean forage and hay samples (<5.1% of the TRR; <0.002 ppm). The only major metabolite was De-Xy-S-2200, which was observed in soybean forage (12.3% of the TRR; 0.005 ppm) from the [Ph-$^{14}$C]-S-2200.

| **Confined Accumulation in Rotational Crops** –Lettuce, wheat, carrot | **PMRA # 2377934** |
|---|---|
| **Test Site** | Each plot consisted of an above-ground plastic sheet-lined wooded container maintained under field condition |
| **Formulation** | The test material was formulated as a 25% suspension concentrate (SC) with an approximate S-2200 R:S isomer ratio of 50:50 |
| **Analytical Method for Overall TRR**<br>**Identification & Characterization** | LSC and combustion<br>HPLC and TLC co-chromatography |
| **Extraction Solvents** | Acetone/water (80:20; v/v); acetone/water/hydrochloric acid (80:20:1; v/v/v) |
| **Post-Extraction Solids (PES)** | Sequential enzyme hydrolysis with Driselase or amylase, mild acid hydrolysis (0.1M HCl, 40°C overnight) and mild base hydrolysis (0.1M NaOH, 40°C overnight), strong acid hydrolysis (6M HCl, 80°C for 4 hours) and strong base hydrolysis (6M NaOH, 80°C for 4 hours) |
| **Storage Stability** | Samples were stored and analyzed within 3 months for carrots. Representative samples of lettuce (6 months) and wheat (9 months) from both radiolabels were re-extracted and analysed to verify the stability of the analytes during freezer storage. Similar profiles were obtained, which indicated stability of [$^{14}$C]-S-2200 metabolites in the tested samples. |
| **Radiolabel Position** | **[Ph-$^{14}$C]-S-2200 and [Bz-$^{14}$C]-S-2200** |

| **Crop/Crop group/*Variety*** | **Rate (g a.i./ha)** | **PBI (days)** | **Growth stage at harvest** | **Harvested RAC** |
|---|---|---|---|---|
| Lettuce/Leafy vegetable/*Salad Bowl* | 1600 | 30, 120, 365 | 50% mature size | Immature heads |
| | | | Maturity | Mature heads |
| Wheat/Cereal grains/*Blanca Royale* | 1600 | 30, 120, 365 | 6-8" to stem elongation | Forage (immature) |
| | | | Early flower to soft dough | Hay |
| | | | Maturity | Grain and straw |
| Carrot/Root vegetable/ *Danvers Half Long 126* | 1600 | 30, 120, 365 | Maturity | Tops (foliage) and roots |

| **Rotational crop sample** | | **Overall TRR (ppm, in S-2200 equivalents)** | | | | | |
|---|---|---|---|---|---|---|---|
| | | **[Ph-$^{14}$C]-S-2200** | | | **[Bz-$^{14}$C]-S-2200** | | |
| | | **30 DAT** | **120 DAT** | **365 DAT** | **30 DAT** | **120 DAT** | **365 DAT** |
| Wheat | Forage | 2.73 | 0.14 | 0.10 | 2.54 | 0.31 | 0.26 |
| | Hay | 1.56 | 0.29 | 0.35 | 4.54 | 0.72 | 0.74 |
| | Straw | 1.32 | 0.34 | 0.31 | 0.82 | 0.59 | 0.38 |
| | Grain | 0.04 | 0.04 | <0.01 | 0.12 | 0.20 | <0.01 |
| Lettuce | Immature | 0.33 | 0.03 | 0.07 | 0.32 | 0.08 | 0.07 |
| | Mature | 0.08 | 0.02 | 0.02 | 0.22 | 0.05 | 0.02 |
| Carrot | Mature roots | 0.05 | 0.03 | <0.01 | 0.04 | 0.04 | <0.01 |
| | Mature foliage | 0.11 | 0.05 | 0.03 | 0.07 | 0.08 | 0.03 |

| Metabolites Identified | | Major Metabolites (>10% of the TRR) | |
|---|---|---|---|
| **Matrices** | **PBI (days)** | **[Ph-$^{14}$C]-S-2200** | **[Bz-$^{14}$C]-S-2200** |
| Immature Lettuce | 30 | 5-$CH_2OH$-S-2200 (conj.), 4-OH-S-2200 (conj.) | 5-$CH_2OH$-S-2200 (conj.), 4-OH-S-2200 (conj.) |
| | 120 | None | 4-OH-S-2200 (conj.) |
| | 365 | S-2200, 4-OH-S-2200 (conj.), 5-$CH_2OH$-S-2200 (conj.) | S-2200, 4-OH-S-2200 (conj.) |
| Mature Lettuce | 30 | S-2200, 4-OH-S-2200 (conj.), 5-$CH_2OH$-S-2200 (conj.) | 4-OH-S-2200 (conj.), 5-$CH_2OH$-S-2200 (conj.) |
| | 120 | None | None |
| | 365 | 4-OH-S-2200 (conj.), 5-$CH_2OH$-S-2200 (conj.) | None |
| Wheat forage | 30 | 2-$CH_2OH$-S-2200 (conj.),<br>4-OH-S-2200 (conj.), 5-$CH_2OH$-S-2200 (conj.) | 5-$CH_2OH$-S-2200 (conj.),<br>4-OH-S-2200 (conj.) |
| | 120 | 4-OH-S-2200 (conj.), 5-$CH_2OH$-S-2200 (conj.) | None |
| | 365 | 5-$CH_2OH$-S-2200 (conj.) | None |
| Wheat hay | 30 | 4-OH-S-2200 (conj.), 5-$CH_2OH$-S-2200 (conj.), 2-$CH_2OH$-S-2200 | 4-OH-S-2200 (conj.) |
| | 120 | 4-OH-S-2200 (conj.), 5-$CH_2OH$-S-2200 (conj.) | None |
| | 365 | None | None |
| Wheat straw | 30/120 | None | None |
| | 365 | None | 4-OH-S-2200 (conj.) |
| Wheat grain | 30/120/365 | Not Profiled[1] | Not Profiled[1] |
| Carrot tops | 30 | None | None |
| | 120 | None | S-2200 |
| | 365 | None | 5-$CH_2OH$-S-2200 (conj.) |
| Carrot roots | 30 | S-2200 | S-2200 |
| | 120 | S-2200<br>2-$CH_2OH$-S-2200 | S-2200 |
| | 365 | Not profiled[1] | Not profiled[1] |

[1] Not profiled due to low total radioactive residues.

Approximately 50 - 90% of the TRR was present in the extractable fraction of the lettuce, wheat and carrot samples from both treatment groups. The results generated in this study demonstrated that there was moderate uptake of radioactive residues in rotational crops seeded in soil 30, 120, and 365 days after treatment with $^{14}$C-S-2200, followed by extensive metabolism to polar metabolites and incorporation into the constituents of the plant. The metabolite De-Xy-S-2200, arising from cleavage of the ether linkage, was found at very low levels only in the benzyl-labelled 30 DAT immature and mature lettuce. Minor metabolites also included MCBX, 5-COOH-S-2200, and free and glycoside conjugates of 2-$CH_2OH$-S-2200, 4-OH-S-2200, and 5-$CH_2OH$-S-2200.

| NATURE OF THE RESIDUE IN LAYING HEN | PMRA # 2377838 |
|---|---|

Two groups of ten laying hens were dosed orally with [Ph$^{14}$C]-S-2200 at 13.37 ppm and [*Bz*-$^{14}$C]-S-2200 at 13.15 ppm in the diet), via gelatin capsule, once daily for 14 days. Samples of excreta were collected daily. Samples of eggs were collected twice daily. The hens were euthanized 6 hours after administration of the final dose.

| | |
|---|---|
| **Formulated Test Substance** | The approximate S-2200 *R:S* isomer ratio was 50:50. |
| **Analytical Method for Overall TRR Identification & Characterization** | LSC and combustion<br>Radio-HPLC using co-chromatography; LC-MS/MS |

| | |
|---|---|
| **Extraction Solvents** | Eggs, fat, and muscle: Sequential extraction with hexane, ethyl acetate, acetonitrile and 1% formic acid in acetonitrile<br>Liver and skin: Sequential extraction with hexane, ethyl acetate, acetonitrile, 1% formic acid in acetonitrile, water, 1M HCl, and 1M ammonia solution |
| **Post-Extraction Solids (PES)** | Liver: Sequential hydrolysis using protease digestion for 18 hours at 37°C, acid hydrolysis with 10M HCl, base hydrolysis with 10M NaOH under reflux |
| **Storage Stability** | Samples were stored and analyzed within 6 months. |

| **Matrices** | **[Ph-$^{14}$C]-S-2200** | | **[Bz-$^{14}$C]-S-2200** | |
|---|---|---|---|---|
| | **TRR (ppm)** | **% of AD** | **TRR (ppm)** | **% of AD** |
| Excreta | - | 83.37 | - | 98.36 |
| Cage wash | - | 1.33 | 0 | 0.99 |
| Muscle (breast) | 0.0127 | 0.007 | 0.025 | 0.014 |
| Muscle (thigh) | 0.0144 | 0.003 | 0.023 | 0.005 |
| Fat (peritoneal) | 0.033 | 0.003 | 0.032 | 0.005 |
| Skin | 0.0478 | 0.003 | 0.0543 | 0.003 |
| Liver | 0.295 | 0.055 | 0.299 | 0.063 |
| Eggs (Day 2-14) | 0.051-0.113 | 0.21 | 0.050-0.081 | 0.18 |

The majority of the administered dose was excreted, with 83% of the total dose of [Ph-$^{14}$C]-S-2200 and 99% of the total dose of [Bz-$^{14}$C]-S-2200 being recovered in the excreta and cage wash. The highest residues were detected in liver and eggs. Following administration of [Ph-$^{14}$C]-S-2200 to hens, total radioactive residues in eggs reached a maximum on day 11 (0.113 ppm). Similarly, following administration of [Bz-$^{14}$C]-S-2200 to hens, total radioactive residues in eggs reached a maximum on day 7 (0.081 ppm). The major residue from laying hen dosed with [Ph-$^{14}$C]-S-2200 and [Bz-$^{14}$C]-S-2200 was S-2200 in fat (33.9-49.5% of the TRR; 0.011-0.016 ppm), and eggs (33.1-51.2% of the TRR; 0.025-0.058 ppm). Another major residue from laying hen dosed with [Ph-$^{14}$C]-S-2200 was 4-OH-S-2200 in liver (13.6% of the TRR; 0.040 ppm). Only S-2200 was confirmed by LC-MS.

All other minor metabolites were only tentatively identified based on chromatographic retention times of metabolite standards. The metabolism of [$^{14}$C]-S-2200 was considered extensive as some tissues contained up to 21 peaks, including diffuse regions of interest. The unextractable radioactivity in liver, remaining after acid, alkaline, and enzymatic hydrolysis (PES), was presumed to be associated mostly with endogenous material, or more polar multi-components.

| **Metabolites identified** | **Major Metabolites (>10% of the TRRs)** | |
|---|---|---|
| **Radiolabel Position** | **[Ph-$^{14}$C]-S-2200** | **[Bz-$^{14}$C]-S-2200** |
| Egg (Day 11) | S-2200 | S-2200 |
| Liver | 4-OH-S-2200 | None |
| Muscle | None | None |
| Skin | None | None |
| Fat | S-2200 | S-2200 |

| **NATURE OF THE RESIDUE IN LACTATING GOAT** | **PMRA # 2377866** |
|---|---|

Two lactating goats were dosed orally with [Ph-$^{14}$C]-S-2200 at 12.65 ppm and [Bz-$^{14}$C]-S-2200 at 14.13 ppm in the diet), via gelatin capsule, once daily for 7 days. Samples of excreta were collected once daily and milk was collected twice daily. The goats were euthanized 6 hours after administration of the final dose.

| | |
|---|---|
| **Formulated Test Substance** | The approximate S-2200 *R:S* isomer ratio was 50:50. |
| **Analytical Method for Overall TRR Identification & Characterization** | LSC and combustion<br>Radio-HPLC using co-chromatography; LC-MS/MS |
| **Extraction Solvents** | Fat, milk fat, muscle: Sequential extraction with hexane, ethyl acetate, acetonitrile and 1% formic acid in acetonitrile<br>Liver and kidney: Sequential extraction with hexane, ethyl acetate, acetonitrile, 1% formic acid in acetonitrile, water, 1M HCl, and 1M ammonia solution |

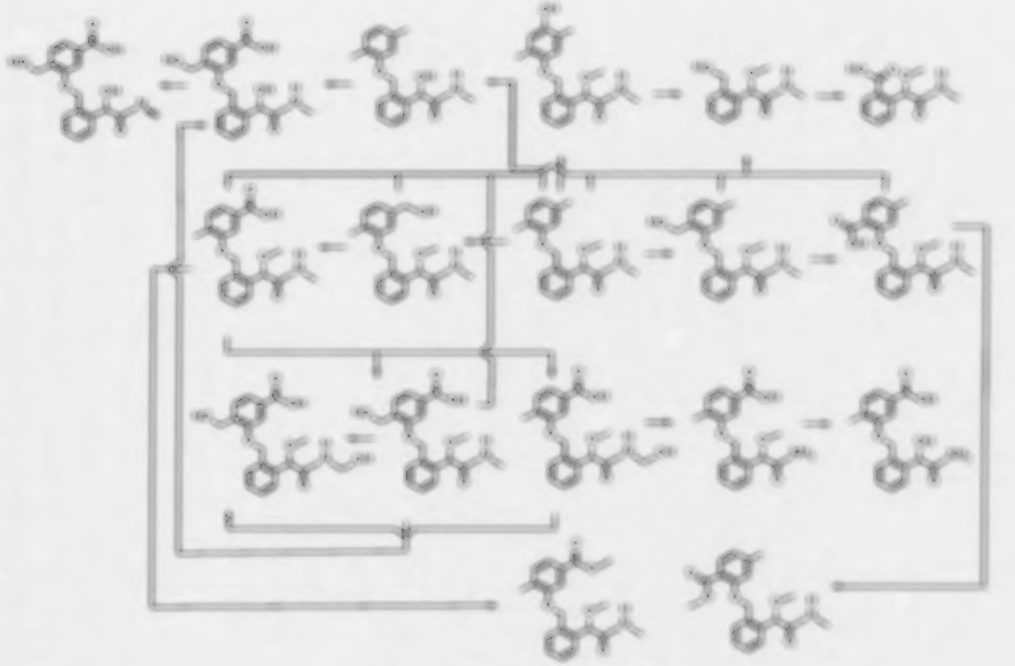
| | |
|---|---|
| **Post-Extraction Solids (PES)** | Liver: Sequential hydrolysis using protease digestion for 18 hours at 37°C, acid hydrolysis with 10M HCl, base hydrolysis with 10M NaOH under reflux. |
| **Storage Stability** | Samples were stored and analysed within 6 months. |

| **Matrices** | **[Ph-$^{14}$C]-S-2200** | | **[Bz-$^{14}$C]-S-2200** | |
|---|---|---|---|---|
| | **TRR (ppm)** | **% of AD** | **TRR (ppm)** | **% of AD** |
| Urine | - | 35.22 | - | 39.75 |
| Cage wash | - | 1.19 | - | 0.68 |
| Feces | - | 42.49 | - | 38.07 |
| Muscle (flank) | 0.012 | 0.005 | 0.016 | 0.003 |
| Muscle (loin) | 0.008 | 0.001 | 0.014 | 0.001 |
| Fat (omental) | 0.012 | 0.006 | 0.028 | 0.002 |
| Fat (renal) | 0.013 | 0.008 | 0.058 | 0.004 |
| Fat (subcutaneous) | 0.010 | 0.001 | 0.033 | <0.001 |
| Kidney | 0.170 | 0.022 | 0.412 | 0.051 |
| Liver | 0.319 | 0.225 | 0.615 | 0.209 |
| Milk – fat fraction | 0.008-0.033 | 0.002 | 0.006-0.035 | 0.005 |
| Milk – aqueous fraction | 0.004-0.010 | 0.024 | 0.006-0.008 | 0.075 |

S-2200 was extensively metabolised and the majority of the administered dose (79% of [Ph-$^{14}$C]-S-2200 and 78% of [Bz-$^{14}$C]-S-2200) was excreted in approximately equal proportions in the urine and faeces. Following administration of [Ph-$^{14}$C]-S-2200 to goats, total radioactive residues in the aqueous fraction of milk reached a maximum on day 6 (0.01 ppm), and on day 7 in the milk fat (0.033 ppm). Similarly, following administration of [Bz-$^{14}$C]-S-2200 to goats, total radioactive residues in the aqueous fraction of milk reached a maximum on day 3 (0.008 ppm) and on day 5 in the milk fat (0.035 ppm). Residues in the tissues, with the exception of the liver, were readily extractable with organic solvents or polar solvents most notably following administration of [Ph-$^{14}$C]-S-2200. The major residue from lactating goat dosed with [Ph-$^{14}$C]-S-2200 and [Bz-$^{14}$C]-S-2200 was S-2200 in fat (22.9-49.6% of the TRR; 0.006-0.007 ppm), muscle (18.2-23.0% of the TRR; 0.002-0.003 ppm), and milk fat fraction (32.7-35.3% of the TRR; 0.011-0.012 ppm); 4-OH-S-2200 (conj.) in kidney (13.3-14.9% of the TRR; 0.025-0.055 ppm), and 5-COOH-S-2200 in kidney (20.2-25.0% of the TRR; 0.043-0.083 ppm), and liver (10.6-19.3% of the TRR; 0.062-0.067 ppm). Other major residues from lactating goat dosed with [Bz-$^{14}$C]-S-2200 were 2-CH$_2$OH-S-2200 in muscle (10.1% of the TRR; 0.002 ppm), and 5-CA-S-2200-NHM in milk (14.7% of the TRR; 0.003 ppm). LC-MS was used to confirm the identity of S-2200 (milk fat, muscle and fat), 2-CH$_2$OH-S-2200 (muscle), 5-COOH-S-2200 (liver and kidney) and 4-OH-S-2200 glucuronide (kidney). All other minor metabolites were only tentatively identified based on chromatographic retention times of metabolite standards. The metabolism of [$^{14}$C]-S-2200 was considered extensive as some tissues contained up to 25 peaks, including diffuse regions of interest. The unextractable radioactivity in liver, remaining after acid, alkaline, and enzymatic hydrolysis (PES), was presumed to be associated mostly with endogenous material, or more polar multi-components.

| **Metabolites Identified** | **Major Metabolites (>10% of the TRR)** | |
|---|---|---|
| **Radiolabel Position** | **[Ph-$^{14}$C]-S-2200** | **[Bz-$^{14}$C]-S-2200** |
| Milk – fat fraction | S-2200 | S-2200 |
| Milk – aqueous fraction | Not analysed | 5-CA-S-2200-NHM |
| Liver | 5-COOH-S-2200 | 5-COOH-S-2200 |
| Kidney | 5-COOH-S-2200, 4-OH-S-2200 (conj.) | 5-COOH-S-2200, 4-OH-S-2200 (conj.) |
| Muscle | S-2200 | S-2200, 2-CH$_2$OH-S-2200 |
| Fat | S-2200 | S-2200 |

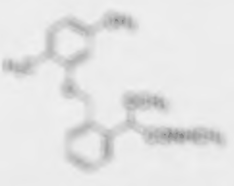
**Proposed Metabolic Pathway of S-2200 in Primary Crops, Secondary Crops, Livestock and Rat**

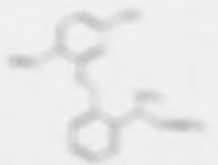
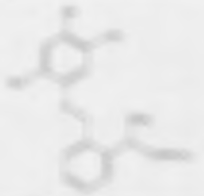
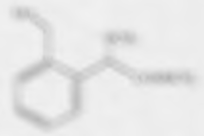
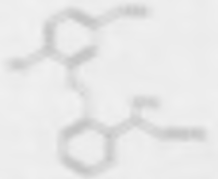


**Major Metabolic Pathways in Primary Crops, Secondary Crops, and Livestock.**

The major metabolic pathways included hydroxylation of the phenoxy ring to form 4-OH-S-2200 and subsequent formation of the glycoside conjugate, and oxidation of the methyl group attached to the phenoxy ring to form 2-CH2OH-S-2200 and 5-CH2OH-S-2200 and their corresponding glycoside conjugates (plants) and glucuronides (livestock). Minor metabolic pathways included the demethylation of the methoxy group of the side chain to form MCBX and cleavage of the ether linkage to form De-Xy-S-2200. In livestock, conjugates are glucuronides.

**Chemical Structure and Codes of Mandestrobin (S-2200) and Major Metabolites Identified in Plant (Primary and Secondary) and Livestock Metabolism Studies**

| Code | Chemical Structure | Found In |
|---|---|---|
| S-2200 |  | **Rat**<br>**Livestock:** ruminant (muscle, fat, milk); poultry (fat, eggs)<br>**Primary Crops:** wheat hay/forage; lettuce (mature and immature), rapeseed seed/forage<br>**Secondary Crops:** lettuce (mature and immature), carrot (roots and foliage) |

| | | |
|---|---|---|
| 2-CH$_2$OH-S-2200 |  | **Rat**<br>**Primary Crops:** wheat hay/forage<br>**Secondary Crops:** carrot roots |
| 4-OH-S-2200 |  | **Rat**<br>**Livestock:** poultry (liver) |
| De-Xy-S-2200 |  | **Rat**<br>**Primary Crops:** wheat grain/straw; soybean forage (seed treatment)<br>**Secondary Crops:** lettuce (mature and immature), carrot (roots and foliage) |
| 5-COOH-S-2200 |  | **Rat**<br>**Livestock:** ruminant (kidney, liver) |
| 4-OH-S-2200 (Bound/ Conjugated/ glycosides) | | **Rat**<br>**Livestock:** ruminant (kidney)<br>**Primary Crops:** rapeseed seed/forage<br>**Secondary Crops:** wheat hay/forage/straw, lettuce (mature and immature) |
| 2-CH$_2$OH-S-2200 (conjugated/glycosides) | | **Primary Crops:** wheat hay/forage; rapeseed forage<br>**Secondary Crops:** wheat forage |
| 5-CH$_2$OH-S-2200 (conjugated/glycosides) | | **Secondary Crops:** wheat hay/forage; lettuce (mature and immature), carrot foliage |

| **Freezer Storage Stability** | | **PMRA # 2277901, 2277903** |
|---|---|---|
| **Matrix** | **Demonstrated storage interval at -18°C (months)** | **Actual storage interval (months)** |
| **Storage stability studies** | | |
| Rapeseed (seed) | 15 and on-going[a] | 38 |
| Rapeseed (oil) | 15 | 10 |
| Rapeseed (meal) | 15 | 6 |
| Lettuce | 15 | No associated residue trial |
| Barley (grain) | 15 | |
| Barley (straw) | 15 | |

| **Concurrent storage stability studies** | | |
|---|---|---|
| Strawberries | 5 and on-going* | 19 |
| Grapes | 8 and on-going* | 16 |
| Grape (juice) | 7 | 7 |
| Grape (raisins) | 5 and on-going* | 9 |
| Soybean (seed) | 12 | 8.3 |
| Corn forage | 12 | 12 |
| Corn K+CWHR | 12 | 11 |
| Corn grain | 12 | 9 |
| Corn stover | 9 | 9 |

In addition, storage stability of incurred $^{14}$C-S-2200 residues in rapeseed forage was investigated over a period of 4 years, and no significant decline of S-2200 was observed.

* Additional storage stability studies to be submitted by applicant at a later date.

**CROP FIELD TRIALS**

Residue trials were conducted throughout Canada and the United States using formulated products (S-2200 2.5 SC, S-2200 4 SC, and S-2200 3.2 FS Fungicide) containing mandestrobin on corn, grapes, soybeans, strawberries, and rapeseed. Adjuvants were added to each spray mixture. Only trial values that were conducted at GAP or within ±25% of GAP were included herein. Residues of S-2200 decline with increasing PHIs in strawberries and grapes. In the case of rapeseeds, the residues declined in one trial, whereas residues were less than LOQ in the other trial.

| **Crop Field Trials on Strawberries (Foliar)** | **PMRA #s 2377911(CDN) and 2377917 (US)** |
|---|---|

**Number and Location of Field Trials**

| **Region** | **1** | **2** | **3** | **5** | **10** | **12** | **Total** |
|---|---|---|---|---|---|---|---|
| **CDN Required*** | 1 | 0 | 0 | 3 | 0 | 1 | **5** |
| **US Required*** | 1 | 0 | 1 | 1 | 2 | 1 | **6** |
| **Submitted** | 1 | 1 | 1 | 3 | 3 | 1 | **10** |

*As per DIR98-02 and USEPA Residue Chemistry Test Guidelines (crop group reduction).

**Use Pattern**

| **Approved Use Pattern (GAP)** | **Study Use Pattern** |
|---|---|
| Single foliar appl. rate: 210-420 g a.i./ha<br># of appl.: 4-5 appl. per year at 7-14 day intervals<br>Maximum rate: 1680 g a.i./ha/season<br>PHI: 0 day | **CDN trials:**<br>Single foliar appl. rate: ~420 g a.i./ha + adjuvant<br># of appl.: 4 appl. per year<br>Maximum rate: 1674-1734 g a.i./ha/season<br>PHI: 0 day |
| | **US trials:**<br>Single foliar appl. rate: ~420 g a.i./ha + adjuvant<br># of appl.: 4 appl. per year<br>Maximum rate: 1675 – 1702 g a.i./ha/season<br>PHI: 0 day<br>Decline Trials: 0, 1, 3, 5 and 7 days |

| **Total Rate (g a.i./ha)** | **PHI (days)** | **S-2200 Residue Levels (ppm)** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **n** | **Min.**[‡] | **Max.**[‡] | **LAFT**[†] | **HAFT**[†] | **Median**[†] | **Mean**[†] | **SD**[†] |
| **US trials** | | | | | | | | | |
| 1675-1702 | 0 | 8 | 0.33 | 2.12 | 0.45 | 2.05 | 0.84 | 0.97 | 0.52 |
| **Canadian trials** | | | | | | | | | |
| 1674-1734 | 0 | 2 | 0.6 | 1.07 | 0.62 | 0.995 | 0.81 | 0.81 | 0.27 |
| **Combined trials** | | | | | | | | | |
| 1674-1734 | 0 | 10 | 0.33 | 2.12 | 0.45 | 2.05 | 0.84 | 0.94 | 0.47 |

[‡] Values based on total number of samples; [†] Values based on per-trial averages; n = number of independent trials.

| **Crop Field Trials on Grapes (Foliar)** | | | | | **PMRA #s 2377913 (CDN) and 2377920 (US)** |
|---|---|---|---|---|---|
| **Number and Location of Field Trials** | | | | | |
| **Region** | 1 | 5 | 10 | 11 | **Total** |
| **CDN Required*** | 0 | 4 | 0 | 1 | **5** |
| **US Required*** | 2 | 0 | 5 | 2 | **9** |
| **Submitted** | 2 | 3 | 7 | 3 | **15** |
| *As per DIR98-02 and USEPA Residue Chemistry Test Guidelines (crop group reduction). | | | | | |

| **Approved Use Pattern (GAP)** | **Study Use Pattern** |
|---|---|
| Single foliar appl. rate: 210-420 g a.i./ha<br># of appl.: 3-4 appl. per year at 10-14 day intervals<br>Maximum seasonal rate: 1260 g a.i./ha<br>PHI: 10 days | **CDN trials:**<br>Single foliar appl. rate: ~420 g a.i./ha + adjuvant<br># of appl.: 3 appl. per year<br>Maximum rate: 1249-1324 g a.i./ha/season<br>PHI: 9-11 days |
| | **US trials:**<br>Single foliar appl. rate: ~420 g a.i./ha + adjuvant<br># of appl.: 3 appl. per year<br>Maximum rate: 1240-1295 g a.i./ha/season<br>PHI: 10 days<br>Decline Trials: 0, 3, 7, 10 and 14 days |

| **Total Rate (g a.i./ha)** | **PHI (days)** | **S-2200 Residue Levels (ppm)** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **n** | **Min.[#]** | **Max.[#]** | **LAFT[*]** | **HAFT[*]** | **Median[*]** | **Mean[*]** | **SD[*]** |
| **US trials** | | | | | | | | | |
| 1240-1295 | 10 | 10 | 0.68 | 3.74 | 0.74 | 3.46 | 1.40 | 1.56 | 0.83 |
| **Canadian trials** | | | | | | | | | |
| 1249-1324 | 9-11 | 4 | 0.44 | 1.13 | 0.47 | 1.08 | 0.86 | 0.82 | 0.29 |
| **Combined trials** | | | | | | | | | |
| 1240-1324 | 9-11 | 14 | 0.44 | 3.74 | 0.47 | 3.46 | 1.19 | 1.37 | 0.79 |
| [#] Values based on total number of samples; [*] Values based on per-trial averages; n = number of independent trials; | | | | | | | | | |

| **Crop Field Trials on Rapeseed (Foliar)** | | | | | | **PMRA #s 2377930 (CDN) and 2377926 (US)** |
|---|---|---|---|---|---|---|
| **Number and Location of Field Trials** | | | | | | |
| **Region** | **1** | **2** | **5** | **7** | **11** | **14** | **Total** |
| **CDN Required*** | 1 | 0 | 1 | 0 | 0 | 14 | **16** |
| **US Required*** | 0 | 1 | 2 | 1 | 2 | 0 | **6** |
| **Submitted** | 0 | 0 | 4 | 2 | 3 | 14 | **23** |
| *As per DIR98-02 and USEPA Residue Chemistry Test Guidelines (crop group reduction). | | | | | | | |

| **Approved Use Pattern (GAP)** | **Study Use Pattern** |
|---|---|
| # of appl.: 1 appl. per year<br>Maximum foliar seasonal rate: 420 g a.i./ha<br>PHI: 35 days | **CDN trials:**<br>Maximum foliar rate: 406-442 g a.i./ha/season + adjuvant<br># of appl.: 3 appl. per year<br>PHI: 31-44 days<br>Decline Trial: 28, 33, 37 and 41 days |
| | **US trials:**<br>Maximum foliar rate: 402-458 g a.i./ha/season + adjuvant<br># of appl.: 1 appl. per year<br>PHI: 34-36 days<br>Decline Trial: 26, 31, 36 and 41 days |

| Total Rate (g a.i./ha) | PHI (days) | S-2200 Residue Levels (ppm) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | n | Min. # | Max. # | LAFT * | HAFT * | Median * | Mean * | SD * |
| **US trials** | | | | | | | | | |
| 402-458 | 34-36 | 12 | <0.02 | 0.13 | <0.02 | 0.125 | <0.02 | 0.03 | 0.04 |
| **Canadian trials** | | | | | | | | | |
| 406-442 | 31-44 | 8 | <0.02 | 0.544 | <0.02 | 0.508 | 0.03 | 0.09 | 0.15 |
| **Combined trials** | | | | | | | | | |
| 402-458 | 31-44 | 20 | <0.02 | 0.544 | <0.02 | 0.508 | 0.02 | 0.07 | 0.12 |

# Values based on total number of samples; * Values based on per-trial averages; n = number of independent trials

| **Crop Field Trials on Field Corn (Seed Treatment)** | **PMRA # 2378153** |
|---|---|
| **Number and Location of Field Trials** | |
| Three (3) trials were conducted at exaggerated rates in Region 5 in NAFTA representative growing regions based on the results of the radiotracer study. | |
| **Approved Use Pattern (GAP)** | **Study Use Pattern** |
| Maximum seasonal rate: 6 g a.i./100 kg seed | Maximum seasonal rate: 3 trials at 10 g a.i./100 kg seed and at 50 g a.i./100 kg seed; Samples were collected between 71-168 days after seed planting. |

| Crop Matrix | Total Rate (g a.i./ha) | PHI (days) | S-2200 Residue Levels (ppm) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | Min. # | Max. # | LAFT * | HAFT * | Median * | Mean * | SD * |
| K+CWHR | 11.6-13.7 (~50 g a.i./ 100 kg seed) | 71-78 | 3 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | -- |
| Forage | | 88-92 | 3 | <0.02 | <0.02 | <0.02 | <0.02 | <0.02 | <0.02 | -- |
| Grain | | 118-168 | 3 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | -- |
| Stover | | 118-168 | 3 | <0.02 | <0.02 | <0.02 | <0.02 | <0.02 | <0.02 | -- |

Residues from the 10 g a.i./100 kg seed application were not analyzed as residues from the 8-fold application rate were all <LOQ. # Values based on total number of samples; * Values based on per-trial averages; n = number of independent trials

| **Crop Field Trials on Soybeans (Seed Treatment)** | **PMRA # 2378152** |
|---|---|
| **Number and Location of Field Trials** | |
| Three (3) trials were conducted at exaggerated rates in Regions 4 (1 trial) and 5 (2 trials) in NAFTA representative growing regions based on the results of the radiotracer study. | |
| **Approved Use Pattern (GAP)** | **Study Use Pattern** |
| Maximum seasonal rate: 10 g a.i./100 kg seed | Maximum seasonal rate: 3 trials at 10 g a.i./100 kg seed and at 50 g a.i./100 kg seed; Samples were collected between 116-136 days after seed planting. |

| Crop Matrix | Total Rate (g a.i./ha) | PHI (days) | S-2200 Residue Levels (ppm) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | Min. # | Max. # | LAFT * | HAFT * | Median * | Mean * | SD * |
| Soybean seed | 21.7-29.1 (~50 g a.i./100 kg seed) | 116-136 | 3 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | -- |

Residues from the 10 g a.i./100 kg seed application were not analyzed as residues from the 5-fold application rate were all <LOQ. # Values based on total number of samples; * Values based on per-trial averages; n = number of independent trials

| **Residue Data in Field Accumulation – Spring, wheat, lettuce, garden beets** | | **PMRA # 2377938, 2377942** |
|---|---|---|
| **Primary Crop** | **Study Use Pattern** | **Rotational Crop (PBIs)** |
| Leaf Lettuce | 1 trial in Region 10 (US) - 4 foliar applications of S-2200 on leaf lettuce for a total of 1696 g a.i./ha | Wheat, spinach, garden beets: (101 DAT/3.8 months)<br>Sorghum, spinach, garden beets: (253 DAT/8.4 months)<br>Wheat, spinach, garden beets: (356 DAT/11.8 months) |

| Commodity | Total Rate (g a.i./ha) | PBI (days) | S-2200 Residue Levels (ppm) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | Min. # | Max. # | LAFT * | HAFT * | Median * | Mean * | SD * |
| Wheat (forage, hay, straw & grain) | 1696 | 101 & 356 | 1 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | -- |
| Spinach | | | 1 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | -- |
| Garden beets (roots and leaves) | | | 1 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | -- |
| Sorghum (forage, stover & grain) | | 253 | 1 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | -- |
| Spinach | | | 1 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | -- |
| Garden beets (roots and leaves) | | | 1 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | -- |

| Primary Crop | Approved Use pattern (GAP) | Study Use Pattern | Rotational Crop (PBIs) |
|---|---|---|---|
| Rapeseed | Maximum foliar rate: 420 g a.i./ha/season (ground and air)<br>Timing: 20-50% bloom<br># of appl.: 1 appl./year<br>PHI: 35 days | 1 trial in Region 7 (US) - 1 foliar application of S-2200 on rapeseed at 415 g a.i./ha (1-fold GAP) | Spring wheat (286 DAT/9.5 months)<br>Garden beets, lettuce (304 DAT/10 months) |

| Commodity | Total Rate (g a.i./ha) | PBI (days) | S-2200 Residue Levels (ppm) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | Min. # | Max. # | LAFT * | HAFT * | Median * | Mean * | SD * |
| Spring Wheat (forage, hay, straw, grain) | 415 | 286 & 304 | 1 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | -- |
| Lettuce | | | 1 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | -- |
| Garden beets (roots and leaves) | | | 1 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | -- |

# Values based on total number of samples; * Values based on per-trial averages; n = number of independent trials.

Based on the results of the field accumulation study, a plant-back interval of 4 months is recommended. Immediate plant-back for labelled-crops.

| **Processed Food and Feed - Grapes** | | **PMRA# 2377920** | |
|---|---|---|---|
| **Test Site** | | One trial in NAFTA Growing Region 10 | |
| **Treatment** | | Broadcast foliar applications | |
| **Rate** | | 6298 g a.i./ha (5-fold GAP) | |
| **End-use product/formulation** | | S-2200 4 SC | |
| **PHI (days)** | | 10 | |
| **Processed Commodities** | | **Average Residues (ppm)** | **Processing Factor** |
| **Grape** | **RAC** | 11.6 | – |
| | **Juice** | 16.2 | 1.4 |
| | **Raisins** | 22.4 | 1.9 |

| **Processed Food and Feed - Rapeseed** | | **PMRA# 2377926** | |
|---|---|---|---|
| **Test Site** | | One trial in NAFTA Growing Region 5 | |
| **Treatment** | | Broadcast foliar applications | |
| **Rate** | | 2095 g a.i./ha (5-fold GAP) | |
| **End-use product/formulation** | | S-2200 4 SC | |
| **PHI (days)** | | 34 | |
| **Processed Commodity** | | **Average Residues (ppm)** | **Processing Factor** |
| **Rapeseed** | **RAC** | 0.23 | – |
| | **Refined oil** | 0.02 | 0.09 |
| | **Meal** | 0.05 | 0.22 |

| **Residues in Livestock Studies** | |
|---|---|
| Residues in livestock studies were not conducted as the only potential livestock feed items from the petitioned uses were rapeseed meal, corn (seed treatment), and rotational crops (sorghum, and wheat), and as such, there was no expectation of quantifiable residues in meat, milk or eggs. In the absence of livestock feeding studies, the metabolism studies (laying hen, lactating goat) can confirm that no finite residues of S-2200 are expected in meat, milk, and eggs. | |
| **Dietary Burden and Anticipated Residues** | **PMRA # 2523426** |
| Dietary burdens of 0.03 ppm (dairy cattle) and 0.008 ppm (poultry) were estimated based on potential livestock feeding items. The anticipated residues in poultry tissues and eggs were calculated to be less than 0.00004 ppm based on the residue-to-feed ratio from the laying hen metabolism study. The anticipated residues in livestock tissues and milk were calculated to be less than 0.00006 ppm based on the residue-to-feed ratio from the lactating goat metabolism study. | |

### Table 9 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

| **Plant Studies** | |
|---|---|
| **Residue Definition for Enforcement**<br>**Residue Definition for Risk Assessment**<br>Primary crops (wheat, lettuce, rapeseed)<br>Rotational crops (wheat, sorghum, lettuce, spinach, beets) | Parent (S-2200) |
| **Metabolic Profile in Diverse Crops** | Plant metabolism studies have been conducted covering the crop categories of cereals, oilseeds and leafy vegetables (except *brassica*). A confined rotational crop study has also investigated the metabolism of residues taken up by wheat, lettuce and carrot. The route of metabolism of S-2200 has been shown to be similar, with the extent of metabolism being greater in commodities harvested at longer pre-harvest intervals. In the primary crop metabolism studies, measurement of the ratio of *R*- and *S*-isomers of S-2200 showed that there was no epimerization of S-2200 at the 2-position of the acetamide moiety. |
| **Animal Studies** | |
| **Animals** | **Ruminant and Poultry** |
| **Residue Definition for Enforcement** | **Not being proposed** |

| | |
|---|---|
| **Residue Definition for Risk Assessment** | In the absence of a livestock feeding study and an enforcement method for animal matrices, and considering that there is no expectation of measurable residues in meat, milk and eggs, based on the anticipated residues, (calculated from the metabolism studies), a residue definition for animal matrices is not being proposed. However, this will be reassessed in the event that there is an expansion of use to a livestock feed item, that contributes significantly to the dietary burden, and livestock feeding studies and enforcement methods are submitted to the Agency. |
| **Metabolic Profile in Animals**<br>(goat, hen) | Mandestrobin is extensively metabolized in livestock. Metabolism studies in laying hens and lactating goats showed that the metabolic pathways in livestock were similar to that found in the rat. |
| **Fat Soluble Residue** | Yes |

**Dietary Risk From Food and Water**

| | **Population** | **Estimated Risk<br>% of Acceptable Daily Intake (ADI)** | |
|---|---|---|---|
| | | **Food Alone** | **Food and Water** |
| **Basic chronic non-cancer dietary exposure analysis**<br>**ADI = 0.3 mg/kg bw/day**<br>**Estimated chronic drinking water concentration = 225 µg/L** | **All infants < 1 year** | 2.1 | 7.7 |
| | **Children 1–2 years** | 7.1 | 9.2 |
| | **Children 3 to 5 years** | 4.2 | 5.9 |
| | **Children 6–12 years** | 1.7 | 3.0 |
| | **Youth 13–19 years** | 0.7 | 1.8 |
| | **Adults 20–49 years** | 0.8 | 2.3 |
| | **Adults 50+ years** | 1.0 | 2.5 |
| | **Females 13-49 years** | 0.9 | 2.4 |
| | **Total population** | 1.3 | 2.8 |

## Table 10 Fate and Behaviour in the Environment

| **Property** | **Test substance** | **Value[1]** | **Transformation products** | **Comments** | **Reference** |
|---|---|---|---|---|---|
| **Abiotic transformation** | | | | | |
| Hydrolysis at 50°C | [Benzyl-$^{14}$C]-S-2200 *R*-isomer, [Benzyl-$^{14}$C]-S-2200 *S*-isomer | pH 4: stable<br>pH 7: stable<br>pH 9: stable | none | Not a route of transformation in the environment | 2377861<br>2377863 |
| Phototransformation on soil | [Benzyl-$^{14}$C]-S-2200 *R*-isomer, [Benzyl-$^{14}$C]-S-2200 *S*-isomer and [Phenoxy-$^{14}$C]-S- | $DT_{50}$ (irradiated) = 52.3-63.8 d;<br>$DT_{90}$ (irradiated) = 173.7-211.8 d;<br>$DT_{50}$ (dark) = 71.7-82.9 | Major: UR*<br>Minor:<br>DX-CA-S-2200;<br>De-Xy-S-2200;<br>2-COOH-S-2200; 5- | Not a route of transformation in the environment; no | 2377867<br>2377864 |

| Property | Test substance | Value[1] | Transformation products | Comments | Reference |
|---|---|---|---|---|---|
|  | 2200 *R*-isomer | d;<br>$DT_{90}$ (dark) = 238.1-275.4 d (SFO) | COOH-S-2200; MCBX; S-2200-OR; $CO_2$ | isomerization occurred |  |
| Phototransformation in water<br>25±1°C | [Benzyl-$^{14}$C]-S-2200 and [Phenoxy-$^{14}$C]-S-2200 *R*-isomer (combined labels) | S-2200 *R*-isomer<br>$DT_{50}$=4.39 d;<br>$DT_{90}$=14.6 d (SFO) (combined labels)<br>Dark: none<br><br>S-2200-OR<br>$DT_{50}$=9.25 d;<br>$DT_{90}$=30.7 d (SFO) | Minor (Benzyl label only):<br>De-Xy-S-2200; $CO_2$<br>Major:<br>S-2200-OR; S-2200-ORC; 2200-PR and $CO_2$.<br>($CO_2$ for phenoxy label, only) | Non-persistent<br><br>Phototransformation is expected to be an important route of dissipation | 2377871 |
|  | [Benzyl-$^{14}$C]-S-2200 *S*-isomer | Irradiated:<br>S-2200 *S*-isomer<br>$DT_{50}$=4.59 d;<br>$DT_{90}$=15.3 d (SFO)<br>Dark: none<br><br>S-2200-OR<br>$DT_{50}$= 8.23 d;<br>$DT_{90}$=27.3 d (SFO) | Major:<br>S-2200-OR; S-2200-ORC; De-Xy-S-2200<br><br>Minor:<br>S-2200-PR; $CO_2$ | Non-persistent<br><br>Phototransformation is expected to be an important route of dissipation | 2377869 |
| Phototransformation in air | Mandestrobin | Mandestrobin is not expected to be volatile under field conditions based on vapour pressure and Henry's law constant. |  |  |  |
| **Biotransformation** |  |  |  |  |  |
| Biotransformation in aerobic soil | [Benzyl-$^{14}$C]-S-2200 *R*-isomer, | California Sand<br>$DT_{50}$: 295 d;<br>$DT_{90}$: 980 d (SFO) | Major:<br>5-COOH-S-2200; $CO_2$; UR<br>Minor:<br>DX-CA-S-2200; 2-COOH-S-2200; 2-CONH$_2$-S-2200; 5-CONH$_2$-S-2200; MCBX; De-Xy-S-2200 | Biotransformation in aerobic soil is a main route of dissipation for mandestrobin | 2377894 |
|  |  | Mississippi Silt loam<br>$DT_{50}$: 393 d;<br>$DT_{90}$: 1867 d (DFOP)<br>Slow $t_{1/2}$ = 635 d | Major:<br>$CO_2$; UR<br>Minor:<br>DX-CA-S-2200; 2-COOH-S-2200; 5-COOH-S-2200; 2-CONH$_2$-S-2200; 5-CONH$_2$-S-2200; MCBX; De-Xy-S-2200 | Mandestrobin is moderately persistent to persistent |  |
|  |  | North Dakota Sandy loam<br>$DT_{50}$: 334 d;<br>$DT_{90}$: 6785 d (IORE)<br>$t_{R\ IORE}$ = 2040 d | Major:<br>5-COOH-S-2200; $CO_2$<br>Minor:<br>DX-CA-S-2200; 2-COOH-S-2200; 2-CONH$_2$-S-2200; 5-CONH$_2$-S-2200; MCBX; De-Xy-S-2200 |  |  |
|  | [Benzyl-$^{14}$C]-S-2200 *R*-isomer | Sandy loam (Speyer 5M)<br>$DT_{50}$: 66.5 d; | Major:<br>5-COOH-S-2200; $CO_2$; UR | Mandestrobin is moderately persistent to | 2377881 |

| Property | Test substance | Value[1] | Transformation products | Comments | Reference |
|---|---|---|---|---|---|
| | | DT$_{90}$: 221 d (SFO) | Minor:<br>DX-CA-S-2200; MCBX; 2-COOH-S-2200; 2,5-DMP | persistent | |
| | | Loamy sand (Speyer 2.2)<br>DT$_{50}$: 238 d;<br>DT$_{90}$: 920 d (DFOP)<br>Slow t$_{1/2}$ = 294 d | Major: none<br>Minor:<br>5-COOH-S-2200; 2-COOH-S-2200; MCBX; DX-CA-S-2200;CO$_2$ | | |
| | | Clay loam (SK920191)<br>DT$_{50}$: 43.3 d;<br>DT$_{90}$: 205 d (DFOP)<br>Slow t$_{1/2}$ = 70 d | Major:<br>5-COOH-S-2200; CO$_2$; UR<br>Minor:<br>2-COOH-S-2200; MCBX; De-Xy-S-2200;DX-CA-S-2200 | | |
| | | Silt loam (Chelmorton)<br>DT$_{50}$: 96.5 d;<br>DT$_{90}$: 631 d (DFOP)<br>Slow t$_{1/2}$ = 230 d | Major:<br>CO$_2$; UR<br>Minor:<br>5-COOH-S-2200; 2-COOH-S-2200; MCBX; DX-CA-S-2200 | | |
| | [Benzyl-$^{14}$C]-S-2200 *R*-isomer | Loam (Aschard)<br>DT$_{50}$: 43.9 d;<br>DT$_{90}$: 213 d (DFOP)<br>Slow t$_{1/2}$ = 77.4 d<br>Silty clay loam (Monteil)<br>DT$_{50}$: 37.5 d;<br>DT$_{90}$: 152 d (IORE)<br>t$_{R\ IORE}$ = 45.8 d | Major:<br>5-COOH-S-2200; CO$_2$; UR<br>Minor:<br>2-COOH-S-2200; MCBX; De-Xy-S-2200;DX-CA-S-220 | Slightly persistent | 2377886 |
| | [Benzyl-$^{14}$C]- and [Phenoxy-$^{14}$C]- S-2200 *R*-isomer | Loam (New Jersey)<br>DT$_{50}$: 110 d;<br>DT$_{90}$: 930 d (DFOP)<br>Slow t$_{1/2}$ = 397 d (combined labels) | Major:<br>DX-CA-S-2200; 5-COOH-S-2200; 2-CONH$_2$-S-2200; 5-CONH$_2$-S-2200; CO$_2$; UR<br>Minor:<br>2-COOH-S-2200; MCBX; De-Xy-S-2200 | Mandestrobin is moderately persistent | 2377890 |
| | [Benzyl-$^{14}$C]-S-2200 *S*-isomer | Loam (New Jersey)<br>DT$_{50}$: 118 d;<br>DT$_{90}$: 1494 d (IORE)<br>t$_{R\ IORE}$ = 450 d | Major:<br>DX-CA-S-2200; 2-CONH$_2$-S-2200; 5-CONH$_2$-S-2200; CO$_2$; UR<br>Minor:<br>2-COOH-S-2200; 5-COOH-S-2200; MCBX; De-Xy-S-2200 | | |

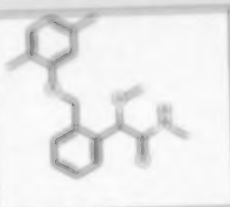
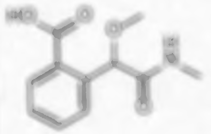
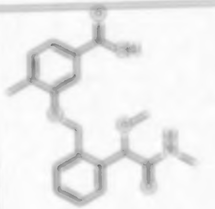
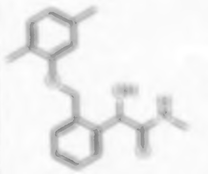
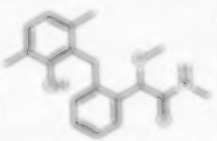
| Property | Test substance | Value[1] | Transformation products | Comments | Reference |
|---|---|---|---|---|---|
|  | [Benzyl-$^{14}$C]-S-2200<br>*S*-isomer | Sandy loam (Speyer 5M)<br>DT$_{50}$: 85.4 d;<br>DT$_{90}$: 284 d (SFO) | Major:<br>5-COOH-S-2200; CO$_2$; UR<br>Minor:<br>2-COOH-S-2200; MCBX; De-Xy-S-2200;DX-CA-S-220 | Mandestrobin is moderately persistent to persistent | 2377883 |
|  |  | Loamy sand (Speyer 2.2)<br>DT$_{50}$: 22305 d;<br>DT$_{90}$: 6599792944837 d (IORE)<br>t$_{R\ IORE}$ = 1.99e+12 d | Major: none<br>Minor:<br>5-COOH-S-2200; 2-COOH-S-2200; MCBX; DX-CA-S-2200; CO$_2$ |  |  |
|  |  | Clay loam (SK920191)<br>DT$_{50}$: 90.2 d;<br>DT$_{90}$: 367 d (DFOP)<br>Slow t$_{1/2}$ = 119 d | Major:<br>5-COOH-S-2200; CO$_2$; UR<br>Minor:<br>2-COOH-S-2200; MCBX |  |  |
|  |  | Silt loam (Chelmorton))<br>DT$_{50}$: 124 d;<br>DT$_{90}$: 730 d (DFOP)<br>Slow t$_{1/2}$ = 261 d | Major:<br>CO$_2$; UR<br>Minor:<br>5-COOH-S-2200; 2-COOH-S-2200; MCBX ;DX-CA-S-2200 |  |  |
|  | [Benzyl-$^{14}$C]-S-2200<br>*S*-isomer | Loam (Aschard)<br>DT$_{50}$: 72.2 d;<br>DT$_{90}$: 266 d (DFOP)<br>Slow t$_{1/2}$ = 83.3 d | Major:<br>5-COOH-S-2200; CO$_2$; UR<br>Minor:<br>2-COOH-S-2200; MCBX; De-Xy-S-2200; DX-CA-S-2200 | Moderately persistent | 2377888 |
|  |  | Silty clay loam (Monteil)<br>DT$_{50}$: 56.5 d;<br>DT$_{90}$: 269 d (IORE)<br>t$_{R\ IORE}$ = 81 d | Major:<br>CO$_2$; UR<br>Minor:<br>5-COOH-S-2200; 2-COOH-S-2200; MCBX; De-Xy-S-2200; DX-CA-S-2200 |  |  |
|  | [Benzyl-$^{14}$C]5-COOH-S-2200 | Silt loam (SK104691)<br>DT$_{50}$: 20.3 d;<br>DT$_{90}$: 89.7 d (IORE)<br>t$_{R\ IORE}$ = 27 d | Major:<br>CO$_2$; UR<br>Minor:<br>DX-CA-S-2200 | Slightly to moderately persistent | 2377879 |
|  |  | Clay loam (SK920191)<br>DT$_{50}$: 24.6 d;<br>DT$_{90}$: 165 d (IORE)<br>t$_{R\ IORE}$ = 49.8 d | Major:<br>CO$_2$; UR<br>Minor: none |  |  |
|  |  | Sandy loam (Speyer 5M)<br>DT$_{50}$: 39.1 d;<br>DT$_{90}$: 161 d (IORE)<br>t$_{R\ IORE}$ = 48.5 d | Major:<br>CO$_2$; UR<br>Minor: none |  |  |

| Property | Test substance | Value[1] | Transformation products | Comments | Reference |
|---|---|---|---|---|---|
|  | [Benzyl-$^{14}$C]2-COOH-S-2200 | Silt loam (SK1046/91)<br>$DT_{50}$: 18.1 d;<br>$DT_{90}$: 60 d (SFO)<br>Clay loam (SK920191)<br>$DT_{50}$: 19.7 d;<br>$DT_{90}$: 73 d (IORE)<br>$t_{R\ IORE}$ = 22 d<br>Sandy loam (Speyer 5M)<br>$DT_{50}$: 27.2 d;<br>$DT_{90}$: 76.9 d (IORE)<br>$t_{R\ IORE}$ = 23.2 d | Major:<br>$CO_2$; UR<br>Minor:<br>DX-CA-S-2200<br>Major:<br>$CO_2$; UR<br>Minor:<br>DX-CA-S-2200<br>Major:<br>$CO_2$; UR<br>Minor:<br>DX-CA-S-2200<br>De-Xy-S-2200 | Slightly to moderately persistent | 2377877 |
| Biotransformation in anaerobic soil | [Benzyl-$^{14}$C]- and [Phenoxy-$^{14}$C]- S-2200 *R*-isomer<br>[Benzyl-$^{14}$C] S-2200 *R*-isomer | Water: loam soil system (New Jersey)<br>$DT_{50}$: 3801 d;<br>$DT_{90}$: 12625 d (SFO)<br>(combined labels)<br>$DT_{50}$: 1795 d;<br>$DT_{90}$: 5963 d (SFO) | Major: UR (New Jersey)<br>Minor:<br>DX-CA-S-2200; 2-COOH-S-2200; 5-COOH-S-2200; De-Xy-S-2200; MCBX; $CO_2$ | Not a route of dissipation for mandestrobin | 2377897 |
|  | [Benzyl-$^{14}$C] S-2200 (1:1, *R:S* isomer ratio) | Water: loamy sand soil system (California)<br>$DT_{50}$: 12,772 d;<br>$DT_{90}$: 42426 d (SFO)<br>Water: sandy loam soil system (North Dakota)<br>$DT_{50}$: 861 d;<br>$DT_{90}$: 2860 d (SFO)<br>Water: silt loam soil system (Mississippi)<br>$DT_{50}$: 1,723 d;<br>$DT_{90}$: 5722 d (SFO) | Major: none (California);<br>Unknown A (North Dakota and Mississippi)<br>Minor:<br>5-COOH-S-2200; 2-COOH-S-2200; DX-CA-S-2200; MCBX; De-Xy-S-2200; $CO_2$ | Not a route of dissipation for mandestrobin | 2377900 |
| **Biotransformation in aerobic water-sediment systems (20±2°C)** | [Benzyl-$^{14}$C]-S-2200 *R*-isomer;<br>[Phenoxy-$^{14}$C]-S-2200 *R*-isomer (combined labels) | Lake water:silt loam sediment<br>$DT_{50}$=322 d<br>$DT_{90}$= 1069 d (SFO)<br>Lake water:loamy sand sediment<br>$DT_{50}$: 781 d;<br>$DT_{90}$: 2803 d (DFOP)<br>Slow $t_{1/2}$ = 870 | Major:<br>5-COOH-S-2200<br>Minor:<br>2-COOH-S-2200, MCBX; $CO_2$<br>Major: none<br>Minor:<br>5-COOH-S-2200; 2-COOH-S-2200, MCBX; $CO_2$ | Partition: 77.9% (at 62 d) and 74.1% in sediment at end of study<br>Partition: 67.8% in sediment at end of study<br>Mandestrobin is persistent | 2377903 |
|  | [Benzyl-$^{14}$C]-S-2200 *S*-isomer | Calwich Abbey Lake water: silt loam sediment<br>$DT_{50}$=161 d<br>$DT_{90}$= 535 d (SFO)<br>Swiss Lake water: | Major:<br>MCBX; UR*<br>Minor:<br>5-COOH-S-2200; $CO_2$<br>Major: none | Partition: 69.6% (at 29 d) and 58.2% in sediment at end of study | 2377905 |

| Property | Test substance | Value¹ | Transformation products | Comments | Reference |
|---|---|---|---|---|---|
| | | loamy sand sediment<br>$DT_{50}$: 733 d;<br>$DT_{90}$: 2435 d (SFO) | Minor:<br>5-COOH-S-2200; 2-COOH-S-2200;<br>MCBX; $CO_2$ | Partition:<br>64.0% in sediment at end of study<br><br>Mandestrobin is moderately persistent to persistent | |
| Biotransformation in anaerobic water-sediment (25°C) | [Benzyl-$^{14}$C]-S-2200 *R*-isomer + [Phenoxy-$^{14}$C]-S-2200 *R*-isomer (combined)<br><br>[Benzyl-$^{14}$C]-S-2200 *S*-isomer | Water clay sediment Brokeh Lake<br>$DT_{50}$: 2,917 d;<br>$DT_{90}$: 9691 d (SFO)<br>(combined label) | ***R*-isomer**<br>Major: UR<br>Minor:<br>MCBX; 5-COOH-S-2200;<br>2,5-DMP; 2-COOH-S-2200;<br>DX-CA-S-2200;<br>De-Xy-S-2200;<br>$CO_2$ | Partition:<br>97.0% in sediment at end of study | 2377907 |
| | | $DT_{50}$: 458 d;<br>$DT_{90}$: 1523 d (SFO) | ***S*-isomer**<br>Major:<br>MCBX<br>Minor:<br>5-COOH-S-2200;<br>2-COOH-S-2200;<br>DX-CA-S-2200; De-Xy-S-2200; DPMBA;<br>$CO_2$ | Partition:<br>68.4% (at 120 d) and 50.7% in sediment at end of study | |
| | | Water sand sediment Golden Lake<br>$DT_{50}$: 8,822 d;<br>$DT_{90}$: 29307 d (SFO)<br>(combined label)<br>$DT_{50}$: 859 d;<br>$DT_{90}$: 2854 d (SFO) | ***R*-isomer**<br>Major: none<br>Minor:<br>MCBX; 5-COOH-S-2200;<br>2,5-DMP; 2-COOH-S-2200;<br>De-Xy-S-2200;<br>$CO_2$<br><br>***S*-isomer**<br>Major:<br>MCBX<br>Minor:<br>5-COOH-S-2200;<br>2-COOH-S-2200;<br>DPMBA; $CO_2$ | Partition:<br>88.3% in sediment at end of study<br><br>Partition:<br>69.5% in sediment at end of study<br><br>Mandestrobin is persistent | |
| **Mobility** | | | | | |
| Adsorption / desorption in soil (5+2 soils) | [Benzyl-$^{14}$C] S-2200 (1:1, *R*:*S* isomer ratio) | $K_F$ = 2.05-18.2 (L/kg-soil)$^{Ads}$<br>$K_{FOC}$ = 287-1104 (L/kg-OC)$^{Ads}$<br>1/n = 0.882-0.962 | | Low to moderately mobile | 2377910<br>2377919 |
| (3 + 3 soils) | [Benzyl-$^{14}$C]-2-COOH-S-2200 | $K_F$ = 0.27-2.94 (L/kg-soil)$^{Ads}$<br>$K_{FOC}$ = 6-226 (L/kg-OC)$^{Ads}$<br>1/n = 0.850-0.922 | | Moderate to very igh mobility | 2377912<br>2377915 |
| (3 + 3 soils) | [Benzyl-$^{14}$C]-5-COOH-S-2200; | $K_F$ = 1.26-8.89 (L/kg-soil)$^{Ads}$<br>$K_{FOC}$ = 29-684 (L/kg-OC)$^{Ads}$<br>1/n = 0.853-1.038 | | Low to very high mobility | 2377914<br>2377916 |
| Adsorption (HPLC) | S-2200 | $K_{OC}$ = 1780 | | Mobity:<br>Low | 2377918 |

| Property | Test substance | Value¹ | Transformation products | Comments | Reference |
|---|---|---|---|---|---|
| | 2-COOH-S-2200<br>5-COOH-S-2200<br>2-CONH$_2$-S-2200<br>5-CONH$_2$-S-2200<br>De-CA-S-2200 | $K_{OC}$ = 18<br>$K_{OC}$ = 19<br>$K_{OC}$ = 122<br>$K_{OC}$ = 172<br>$K_{OC}$ = 18 | | Very high<br>Very high<br>High<br>Moderate<br>Very high | |
| 6-years lysimeter study (2 lysimeters) | [Benzyl-$^{14}$C]-S-2200 250SC | Silty sand soil<br>0.26% and 0.43% AR recovered in leachate | De-Xy-S-2200,<br>DX-CA-S-2200,<br>2-COOH-S-2200,<br>5-COOH-S-2200,<br>MC105 | Low leaching / mobility potential | 2377921 |
| Volatilization | Not required based on the low vapour pressure ($3.36 \times 10^{-8}$ Pa at 20°C) and Henry's law constant ($6.5 \times 10^{-12}$ atm m$^3$/mol) | | | | |
| **Field studies** | | | | | |
| Saskatchewan<br>Bare soil | S-2200 4SC | Loam<br>$DT_{50}$ 1.04 d,<br>$DT_{90}$: 367 d (DFOP)<br>Slow $t_{1/2}$ = 163 d | Minor<br>DX-CA-S-2200,<br>2-COOH S-2200<br>5-COOH S-2200 | No residues beyond 30 cm soil depth<br>Mandestrobin is non-persistent in soil | 2377953 |
| North Dakota<br>Bare ground | S-2200 4SC | Loam:<br>$DT_{50}$: 4.89 d,<br>$DT_{90}$: 2015 d (IORE)<br>$t_{R\ IORE}$ = 606 d or 142 (excluding outlier at 303 d) | Minor<br>DX-CA-S-2200,<br>2-COOH S-2200<br>5-COOH S-2200 | No residues beyond 15 cm soil depth.<br>Mandestrobin is non-persistent in soil | 2377968 |
| Ontario, Canada<br>Bare ground | S-2200 4SC | Sandy loam:<br>$DT_{50}$ = 83.9 d,<br>$DT_{90}$: 486 d (DFOP)<br>Slow $t_{1/2}$ = 173 d | Minor<br>DX-CA-S-2200,<br>2-COOH S-2200<br>5-COOH S-2200 | No residues beyond 15 cm soil depth and Mandestrobin is moderately persistent in soil | 2495782 |
| Field dissipation Established Turfgrass in Ontario, Canada | S-2200 4SC | Turf/Thatch:<br>$DT_{50}$: 8.43 d,<br>$DT_{90}$: 28 d (SFO)<br><br>Sandy loam soil:<br>$DT_{50}$:43.3 d,<br>$DT_{90}$: 380 d (IORE)<br>$t_{R\ IORE}$ = 114 d | Minor<br>De-Xy- S-2200,<br><br>Minor<br>2-COOH S-2200<br>5-COOH S-2200 | No residues beyond 30 cm soil depth.<br><br>Mandestrobin is non-persistent to slightly persistent | 2377963 |
| **Bioconcentration/bioaccumulation** | | | | | |
| Bioconcentration and Metabolism with Bluegill Sunfish (*Lepomis macrochirus*) | [Benzyl-$^{14}$C]S-2200 | Whole body steady state Bioconcentration factor = 23-26<br><br>Kinetics for S-2200 was not calculated | Transformation products formed by hydroxylation then conjugated with sulfate and glucuronic acid | depuration half-life for the total radioactive residues ~2 days | 2378049 |
| ¹ Kinetics models: SFO = single first-order; IORE = indeterminate order rate equation; DFOP = double first order in parallel.<br>*UR: unextracted residues | | | | | |

**Table 11 Major Transformation Products Formed in the Environment**

| Code | Chemical name | Chemical structure | Study | max %AR (day) | %AR at Study End (study length) | References |
|---|---|---|---|---|---|---|
| **PARENT** | | | | | | |
| S-2200 | (RS)-2-methoxy-N-methyl-2-[α-(2,5-xylyloxy)-o-tolyl]acetamide |  | | | | |
| **MAJOR (>10%) TRANSFORMATION PRODUCTS** | | | | | | |
| DX-CA-S-2200 | (RS)-2-(N-methylcarbamoyl-methoxymethyl) benzoic acid |  | Aerobic soil | 11.0 (151) | 8.8 (362) | 2377800 |
| | | | Anaerobic soil | 6.2 (200) | 0 (365) | 2377807 |
| | | | Soil photolysis | 6.7 (17) | 6.3 (30) | 2377864 |
| | | | Aqueous photolysis | – | – | – |
| | | | Hydrolysis | – | – | – |
| | | | Aerobic aquatic | – | – | – |
| | | | Anaerobic aquatic | 0.37 (120) | 0.16 (357) | 2377807 |
| | | | Field studies | 5.3 (59) | 0 (620) | 2377833 |
| 5-COOH-S-2200 | (RS)-3-{2-[1-methoxy-1-(N-methylcarbamoyl)methyl]benzyloxy}-4-methylbenzoic acid |  | Aerobic soil | 10 (59) | 12.6 (120) | 2377800 |
| | | | Anaerobic soil | 8.8 (67) | 7.9 (365) | 2377807 |
| | | | Soil photolysis | – | – | – |
| | | | Aqueous photolysis | – | – | – |
| | | | Hydrolysis | – | – | – |
| | | | Aerobic aquatic | 11.9 (62) | 2 (100) | 2377805 |
| | | | Anaerobic aquatic | 1.58 (240) | 0 (365) | 2377807 |
| | | | Field studies | 6.8 (28) | 0 (670) | 2377833 |
| MCBX | (RS)-2-hydroxy-N-methyl-2-[α-(2,5-xylyloxy)-o-tolyl]acetamide |  | Aerobic soil | 2.8 (15) | 0.7 (366) | 2377806 |
| | | | Anaerobic soil | 7.3 (316) | 7.3 (316) | 2377800 |
| | | | Soil photolysis | 0.9 (17) | 0.6 (30) | 2377864 |
| | | | Aqueous photolysis | – | – | – |
| | | | Hydrolysis | – | – | – |
| | | | Aerobic aquatic | 98.8 (102) | 98.1 (102) | 2377805 |
| | | | Anaerobic aquatic | 32.08 (357) | 32.08 (357) | 2377807 |
| | | | Field studies | – | – | – |
| S-2200-GR | (RS)-2-[2-(2-hydroxy-3,6-dimethylbenzyl)phenyl]-2-methoxy-N-methylacetamide |  | Aerobic soil | – | – | – |
| | | | Anaerobic soil | – | – | – |
| | | | Soil photolysis | 1.8 (30) | 1.8 (30) | 2377864 |
| | | | Aqueous photolysis | 26.5 (7) | 8.5 (30) | 2377871 |
| | | | Hydrolysis | – | – | – |
| | | | Aerobic aquatic | – | – | – |
| | | | Anaerobic aquatic | – | – | – |
| | | | Field studies | – | – | – |
| S-2200- | (RS)-N,1,6- | | Aerobic soil | – | – | – |

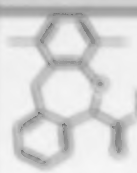
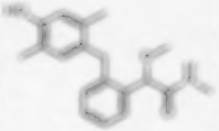
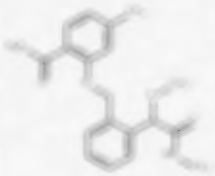
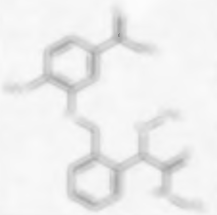
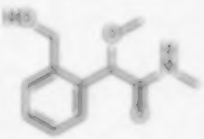
| Code | Chemical name | Chemical structure | Study | max % AR (day) | % AR at Study End (study length) | References |
|---|---|---|---|---|---|---|
| [illegible] | [illegible]-dihydrodibenzo [b,e]oxepine-6-carboxamide |  | Anaerobic soil | - | - | - |
| | | | Soil photolysis | - | - | - |
| | | | Aqueous photolysis | [illegible] | [illegible] | [illegible] |
| | | | Hydrolysis | - | - | - |
| | | | Aerobic aquatic | - | - | - |
| | | | Anaerobic aquatic | - | - | - |
| | | | Field studies | | | |
| [illegible] | (RS)-2-[2-(4-hydroxy-2,5-dimethylbenzyl)phenyl]-2-methoxy-N-methylacetamide |  | Aerobic soil | - | - | - |
| | | | Anaerobic soil | - | - | - |
| | | | Soil photolysis | - | - | - |
| | | | Aqueous photolysis | [illegible] | [illegible] | [illegible] |
| | | | Hydrolysis | - | - | - |
| | | | Aerobic aquatic | - | - | - |
| | | | Anaerobic aquatic | - | - | - |
| | | | Field studies | - | - | - |
| [illegible] | 2-({2-[1-methoxy-2-(methylamino)-2-oxoethyl]benzyl}oxy)-4-methylbenzamide |  | Aerobic soil | [illegible] | [illegible] | [illegible] |
| | | | Anaerobic soil | - | - | - |
| | | | Soil photolysis | - | - | - |
| | | | Aqueous photolysis | - | - | - |
| | | | Hydrolysis | - | - | - |
| | | | Aerobic aquatic | - | - | - |
| | | | Anaerobic aquatic | - | - | - |
| | | | Field studies | | | |
| [illegible] | 5-({2-[1-methoxy-2-(methylamino)-2-oxoethyl]benzyl}oxy)-4-methylbenzamide |  | Aerobic soil | [illegible] | [illegible] | [illegible] |
| | | | Anaerobic soil | - | - | - |
| | | | Soil photolysis | - | - | - |
| | | | Aqueous photolysis | - | - | - |
| | | | Hydrolysis | - | - | - |
| | | | Aerobic aquatic | - | - | - |
| | | | Anaerobic aquatic | - | - | - |
| | | | Field studies | - | - | - |
| [illegible] | (RS)-2-[2-(hydroxymethyl)phenyl]-2-methoxy-N-methylacetamide |  | Aerobic soil | [illegible] | [illegible] | [illegible] |
| | | | Anaerobic soil | [illegible] | [illegible] | [illegible] |
| | | | Soil photolysis | [illegible] | [illegible] | [illegible] |
| | | | Aqueous photolysis | [illegible] | [illegible] | [illegible] |
| | | | Hydrolysis | - | - | - |
| | | | Aerobic aquatic | - | - | - |
| | | | Anaerobic aquatic | [illegible] | [illegible] | [illegible] |
| | | | Field studies | - | - | - |

**Table 12** **Toxicity of Mandestrobin and Transformation Products to Non-Target Terrestrial Species**

| Organism | Exposure | Test substance | Endpoint value | Degree of toxicity[1] | Reference |
|---|---|---|---|---|---|
| **Invertebrates** | | | | | |
| Earthworm, *Eisenia fetida* | 14-d Acute | S-2200 TG | $LC_{50}$> 168 mg a.i./kg soil dw | n/a | 2378014 |
| | | 2-COOH-S-2200 | 14-d $LC_{50}$>1000 mg /kg soil dw (highest concentration tested) | n/a | 2378015 |
| | | 5-COOH-S-2200 | $LC_{50}$>1000 mg /kg soil dw (highest concentration tested) | n/a | 2378016 |
| | 56-d Chronic | S-2200 TG | NOEC = 7.5 mg a.i./kg soil dw | n/a | 2378021 |
| Honeybee , *Apis mellifera* | Acute oral | S-2200 TG | $LD_{50}$ >110.71 µg a.i./bee (highest dose tested) | Practically non-toxic | 2378017 |
| | Acute contact | S-2200 TG | $LD_{50}$ >100 µg a.i./bee (highest dose tested) | Practically non-toxic | 2378017 |
| Honeybee, *Apis mellifera* Larva | Acute | S-2200 TG | $LD_{50}$ >100 µg a.i./larva (highest dose tested) | n/a | 2378018 |
| Predatory mite, *Typhlodromus pyri Scheuten* | 7-d Contact, Glass plates | S-2200 25SC | $LR_{50}$ > 1000 g a.i./ha<br>$ER_{50}$ (reproduction) > 1000 g a.i./ha (highest rate tested) | n/a | 2378019 |
| Parasitoid, *Aphidius rhopalosiphi* | 48h-Contact, Glass plates | S-2200 25SC | 48-h $LR_{50}$ > 1000 g a.i./ha (highest rate tested)<br>48 h-$ER_{50}$ (reproduction) = 757.2 g a.i./ha | n/a | 2378020 |
| **Birds** | | | | | |
| Bobwhite quail, *Colinus virginianus* | Acute Oral | S-2200 TG | 14-d $LD_{50}$ >2250 mg a.i./kg bw (highest concentration tested) | Practically non-toxic | 2378050 |
| Canary, *Serinus canaria* | | S-2200 TG | 14-d $LD_{50}$ >1000 mg a.i./kg bw | non-toxic at the highest dose with no regurgitation | 2378051 |
| Bobwhite quail, *Colinus virginianus* | 5-d Dietary | S-2200 TG | 8-d $LC_{50}$ >5620 mg a.i./kg diet (>1136 mg a.i./kg bw/day) (highest concentration tested) | Practically non-toxic | 2378052 |
| Mallard duck, *Anas platyrhynchos* | | S-2200 TG | 8-d $LC_{50}$ >5620 a.i./kg diet (>2460 mg a.i./kg bw/day) (highest concentration tested) | Practically non-toxic | 2378053 |
| Bobwhite quail *Colinus virginianus* | 21-w Reproduction | S-2200 TG | 21-w NOEC = 1000 mg a.i./kg diet (91.1 mg a.i./kg bw/day) | n/a | 2378055 |

| Organism | Exposure | Test substance | Endpoint value | Degree of toxicity[1] | Reference |
|---|---|---|---|---|---|
| Mallard duck, *Anas platyrhynchos* | 20-w Reproduction | S-2200 TG | 20-w NOEC = 1000 mg a.i./kg diet (129.1 mg a.i./kg bw/day) | n/a | 2378057 |
| **Mammals** | | | | | |
| Rat | Acute | S-2200 TG | $LD_{50}$ >2000 mg a.i./kg bw (highest concentration tested) | Practically non-toxic | 2377929 |
| | 2-generation reproduction | S-2200 TG | NOAEL (offspring) = 300[illegible]ppm (166/195 mg/kg bw/d ♂/♀) | n/a | 2377964<br>2525908 |
| **Vascular plants** | | | | | |
| Four monocots: onion, ryegrass, wheat and corn. | Seedling Emergence | S-2200 4 SC | $EC_{25}$ >560 g a.i./ha<br>NOEC = 560 g a.i./ha (highest rate tested) | n/a | 2378070 |
| Six dicots: sugarbeet, oilseed rape, cabbage, soybean, lettuce and tomato. | Vegetative Vigor | S-2200 4 SC | $EC_{25}$ >560 g a.i./ha<br>NOEC = 560 g a.i./ha (highest rate tested) | n/a | 2378071 |

[1] Atkins *et al.* (1981) for bees and USEPA classification for others, where applicable; n/a, not applicable

**Table 13 Screening Level and Refined Risk Assessment of Mandestrobin for Non-Target Species, Other than Birds and Mammals**

| Organism | Exposure | Endpoint Value | EEC | RQ | Level of Concern |
|---|---|---|---|---|---|
| **Invertebrates** | | | | | |
| Earthworm | Acute | $LC_{50}/2$: 84 mg a.i./kg soil | 0.844 mg a.i./kg soil | 0.01 | Not exceeded |
| Bee | Contact | $LD_{50}$: > 100 µg a.e./bee | 0. 472 kg a.i/ha × 2.4 µg a.i./bee per kg/ha = 1.13 µg a.i./bee | < 0.01 | Not exceeded |
| | Oral | $LD_{50}$: > 110.71 µg a.i./bee | 0. 472 kg a.i./ha × 29 µg a.i./bee per kg/ha = 13.7 µg a.i./bee | < 0.1 | Not exceeded |
| | Larva acute | $LD_{50}$: > 100 µg a.i./larva | 0. 472 kg a.i./ha × 29 µg a.i./bee per kg/ha = 13.7 µg a.i./larva | <0.1 | Not exceeded |
| Predatory arthropod, *Typhlodromus pyri* | Contact, glass plate | $LR_{50}$: > 1000 g a.i./ha | In-field: 472 g a.i./ha<br>Cumulative rate of 744.4 g a.i./ha | In-field: < 0.7 | Not exceeded |
| Parasitoid arthropod, *Aphidius rhopalosiphi* | Contact, glass plate | $LR_{50}$: > 1000 g a.i./ha | | | |

| Organism | Exposure | Endpoint Value | EEC | RQ | Level of Concern |
|---|---|---|---|---|---|
| **Vascular plants** | | | | | |
| Vascular plant | Seedling emergence; Vegetative vigour | $ER_{25}$: >560 g a.i./ha | In-field: 472 g a.i./ha Cumulative rate of 744.4 g a.i./ha | In-field: <1.3 | Exceeded[1] |
| | | | Off-field (aerial appl., 17% drift): 80.24 g a.i./ha; cumulative rate of 126.55 g a.i./ha | Off-field (aerial): <0.2 | Not exceeded |

[1] The cumulative rate (744.4 g a.i/ha) based on foliar dissipation was used and $ER_{25}$ was >560 g a.i./ha as the maximum seasonal rate was not tested in studies.

**Table 14 Screening Level Risk Assessment of Foliar Application of Mandestrobin for Birds and Mammals**

| | Toxicity (mg a.i./kg bw/d) | Feeding Guild (food item) | EDE* (mg a.i./kg bw) | RQ | Level of Concern |
|---|---|---|---|---|---|
| **Small Bird (0.02 kg)** | | | | | |
| Acute | >100.00 | Insectivore | 60.59 | <0.6 | Not exceeded |
| Reproduction | 91.10 | Insectivore | 60.59 | 0.7 | Not exceeded |
| **Medium Sized Bird (0.1 kg)** | | | | | |
| Acute | >100.00 | Insectivore | 47.28 | <0.5 | Not exceeded |
| Reproduction | 91.10 | Insectivore | 47.28 | 0.5 | Not exceeded |
| **Large Sized Bird (1 kg)** | | | | | |
| Acute | >100.00 | Herbivore (short grass) | 30.54 | <0.3 | Not exceeded |
| Reproduction | 91.10 | Herbivore (short grass) | 30.54 | 0.3 | Not exceeded |
| **Small Mammal (0.015 kg)** | | | | | |
| Acute | >200.00 | Insectivore | 34.85 | <0.2 | Not exceeded |
| Reproduction | 166 | Insectivore | 34.85 | 0.2 | Not exceeded |
| **Medium Sized Mammal (0.035 kg)** | | | | | |
| Acute | >200.00 | Herbivore (short grass) | 67.59 | <0.3 | Not exceeded |
| Reproduction | 166 | Herbivore (short grass) | 67.59 | 0.4 | Not exceeded |
| **Large Sized Mammal (1 kg)** | | | | | |
| Acute | >200.00 | Herbivore (short grass) | 36.12 | <0.2 | Not exceeded |
| Reproduction | 166 | Herbivore (short grass) | 36.12 | 0.2 | Not exceeded |

*EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/bw) × EEC, where:
FIR: Food Ingestion Rate. For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:
Passerine Equation (body weight <or = 200 g): FIR (g dry weight/day) = 0.398 (bw in g)$^{0.850}$
All birds Equation (body weight >200 g): FIR (g dry weight/day) = 0.648 (bw in g) 0.651
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235 (bw in g)$^{0.822}$
bw: Generic Body Weight
EEC: Concentration of pesticide on food item. At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

## Table 15 Screening Level Assessment of Seed Treatment with Mandestrobin for Birds and Mammals

| | Study Endpoint (mg a.i./kg bw/day/UF) | EDE* (mg a.i./kg bw/day) | RQ | Level of concern |
|---|---|---|---|---|
| **Small bird (0.02 kg** | | | | |
| Acute | 100.00 | 25.394 | 0.3 | Not exceeded |
| Reproduction | 91.10 | 25.394 | 0.3 | Not exceeded |
| **Medium bird (0.10 kg)** | | | | |
| Acute | 100.00 | 19.947 | 0.2 | Not exceeded |
| Reproduction | 91.10 | 19.947 | 0.2 | Not exceeded |
| **Large bird (1.00 kg)** | | | | |
| Acute | 100.00 | 5.815 | 0.1 | Not exceeded |
| Reproduction | 91.10 | 5.815 | 0.1 | Not exceeded |
| **Small mammals (0.015 kg)** | | | | |
| Acute | 200.00 | 14.512 | 0.1 | Not exceeded |
| Reproduction | 166 | 14.512 | 0.3 | Not exceeded |
| **Medium mammals (0.035 kg)** | | | | |
| Acute | 200.00 | 12.480 | 0.1 | Not exceeded |
| Reproduction | 166 | 12.480 | 0.2 | Not exceeded |
| **Large mammals (1.00 kg)** | | | | |
| Acute | 200.00 | 6.872 | 0.03 | Not exceeded |
| Reproduction | 166 | 6.872 | 0.1 | Not exceeded |

*EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/bw) × EEC, where:

FIR: Food Ingestion Rate. For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200g, the "all birds" equation was used:

Passerine Equation (body weight <or = 200 g): FIR (g dry weight/day) = 0.398 (bw in g)$^{0.850}$

All birds Equation (body weight >200 g): FIR (g dry weight/day) = 0.648 (bw in g) 0.651

For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235 (bw in g)$^{0.822}$

bw: Generic Body Weight

EEC: Concentration of pesticide on food item. At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

## Table 16 Toxicity of Mandestrobin, S-2200-*R*-Isomer, S-2200-*S*-Isomer and Transformation Products to Non-Target Aquatic Species

| Organism | Exposure | Test substance | Endpoint value | Degree of toxicity[1] | Reference |
|---|---|---|---|---|---|
| **Freshwater species** | | | | | |
| Water flea, *Daphnia magna* | 48-h Acute | S-2200 TG | $EC_{50}$ = 1.2 mg a.i./L | Moderately toxic | 2378022 |
| | | S-2200 (*R*-Isomer) | $EC_{50}$ = 0.92 mg/L | Highly toxic | 2378026 |
| | | S-2200 (*S*-Isomer) | $EC_{50}$ > 14 mg/L | Slightly toxic at the highest concentration tested | 2378027 |
| | | 2-COOH-S-2200 | $EC_{50}$ > 100 mg/L | Practically non-toxic at the highest concentration tested | 2378023 |
| | | 5-COOH-S-2200 | $EC_{50}$ > 100 mg/L | Practically non-toxic at the highest | 2378024 |

| Organism | Exposure | Test substance | Endpoint value | Degree of toxicity[1] | Reference |
|---|---|---|---|---|---|
| | | | | concentration tested | |
| | | S-2200 -OR | EC$_{50}$ > 14 mg | Slightly toxic at the highest concentration tested | 2378028 |
| | | S-2200 -ORC | EC$_{50}$ > 2.5 mg/L | Moderately toxic up to the limit of solubility of the test | 2378025 |
| | 21-d Chronic | S-2200 TG | NOEC = 0.56 mg a.i./L | n/a | 2378029 |
| Sediment dwelling invertebrate, *Chironomus dilutus* | 65-d Chronic | S-2200 TG | NOEC = 3.0 mg a.i./kg dw sediment, 4.93 mg a.i./L porewater | n/a | 2378036 |
| Sediment dwelling invertebrate, *Chironomus riparius* | 28-d Chronic | S-2200 TG | NOEC = 8.1 mg a.i./L | n/a | 2378033 |
| Amphipod, *Hyalella azteca* | 42-d Life cycle | S-2200 TG | NOEC = 5.0 mg a.i./kg dw sediment and<br>6.38 mg a.i./L in pore water | n/a | 2378035 |
| Rainbow trout, *Oncorhynchus mykiss* | 96-h Acute | S-2200 TG | LC$_{50}$ = 0.93 mg a.i./L | Highly toxic | 2378037 |
| | | S-2200 (*R*-Isomer) | LC$_{50}$ = 0.84 mg/L | Highly toxic | 2378038 |
| | | S-2200 (*S*-Isomer) | LC$_{50}$ >12 mg/L (highest concentration tested) | Slightly toxic | 2378039 |
| | | 2-COOH-S-2200 | LC$_{50}$ >89 mg/L (highest concentration tested) | Slightly toxic | 2378040 |
| | | 5-COOH-S-2200 | LC$_{50}$ >100 mg/L (highest concentration tested) | Practically non toxic | 2378041 |
| | | S-2200 -OR | LC$_{50}$ >9.0 mg/L (highest concentration tested) | Moderately toxic | 2378042 |
| | | S-2200 -ORC | LC$_{50}$ >1.4 mg/L (highest concentration with on precipitate) | Moderately toxic | 2378043 |
| Bluegill sunfish, *Lepomis macrochirus*) | 96-h Acute | S-2200 TG | LC$_{50}$ = 2.4 mg a.i./L | Moderately toxic | 2378044 |
| Fathead minnow, *Pimephales promelas* | 96-h Acute | S-2200 TG | LC$_{50}$ = 1.0 mg a.i./L | Highly toxic | 2378045 |
| Fathead minnow, (*Pimephales promelas*) | 28-d Chronic | S-2200 TG | NOEC = 0.15 mg a.i./L<br>(28 days post-hatch) | n/a | 2378047 |
| Green algae, *Pseudokirchneriella subcapitata* | 96-h Acute | S-2200 TG | EC$_{50}$ = 0.39 mg a.i./L (inhibition) | n/a | 2378060 |
| | 72-h Acute | S-2200 (*R*-Isomer) | E$_b$C$_{50}$ = 0.38 mg/L | n/a | 2378067 |

| Organism | Exposure | Test substance | Endpoint value | Degree of toxicity[1] | Reference |
|---|---|---|---|---|---|
| | | S-2200 (*S*-Isomer) | $E_bC_{50}$ >12 mg/L (highest concentration tested) | n/a | 2378068 |
| | | 2-COOH-S-2200 | $E_bC_{50}$ =58 mg/L | n/a | 2378061 |
| | | 5-COOH-S-2200 | $E_bC_{50}$ >54 mg/L (highest concentration tested) | n/a | 2378062 |
| | | S-2200 -OR | $E_bC_{50}$ >9.9 mg/L (highest concentration tested) | n/a | 2378063 |
| | | S-2200 -ORC | $E_bC_{50}$ >5.0 mg/L (highest concentration tested) | n/a | 2378059 |
| Blue-green algae, *Anabaena flos-aquae* | 96-h Acute | S-2200 TG | $EC_{50}$ = 0.065 mg a.i./L (yield)<br>NOEC = 0.023 mg a.i./L (algistatic) | n/a | 2378065 |
| Diatom, *Navicula pelliculosa* | 96-h Acute | S-2200 TG | $EC_{50}$ = 1.7 mg a.i./L<br>NOEC = 1.1 mg a.i./L | n/a | 2378066 |
| Monocot vascular plant, duckweed, *Lemna gibba* | 7-d Dissolved | S-2200 TG | $EC_{50}$ > 2.3 mg a.i./L<br>NOEC = 0.32 mg a.i./L (Frond number) | n/a | 2378072 |
| **Marine/estuarine species** | | | | | |
| Crustacean, mysid shrimp, *Americamysis bahia* | 96-h Acute | S-2200 TG | $LC_{50}$ = 0.43 mg a.i./L | Highly toxic | 2378031 |
| | 36-d Chronic | S-2200 TG | NOEC = 0.049 mg a.i./L | n/a | 2378032 |
| Sediment-dwelling amphipod, *Leptocheirus plumulosus* | 28-d Chronic | S-2200 TG | NOEC = 10.3 mg a.i./kg dw sediment, 1.56 mg a.i./L porewater | n/a | 2378034 |
| Mollusk, Eastern oyster, *Crassostrea virginica* | 96-h Acute | S-2200 TG | $EC_{50}$ = 2.0 mg a.i./L | Moderately toxic | 2378030 |
| Sheepshead minnow, *Cyprinodon variegatus* | 96-h Acute | S-2200 TG | $LC_{50}$ >2.2 mg a.i./L | Moderately toxic | 2378046 |
| | 28-d Chronic | S-2200 TG | NOEC = 0.64 mg a.i./L (28 days post-hatch) | n/a | 2378048 |
| Marine diatom, *Skeletonema costatum* | 96-h Acute | S-2200 TG | $EC_{50}$ = 0.5 mg a.i./L<br>NOEC = 0.18 mg a.i./L (yield) | n/a | 2378069 |

[1] USEPA classification, where applicable; n/a, not applicable

## Table 17 Screening Level Risk Assessment of Mandestrobin to Aquatic Organisms

| Organism | | Exposure | Endpoint Value (mg a.i./L) | EEC (mg a.i./L) | RQ | Level of Concern |
|---|---|---|---|---|---|---|
| **Freshwater species** | | | | | | |
| Invertebrates (*Daphnia magna*) | | Acute | EC$_{50}$/2: 0. 6 | 0.24 | 0.4 | Not exceeded |
| | | Chronic | NOEC: 0.56 | 0.24 | 0.4 | Not exceeded |
| Sediment Invertebrate *(Chironomus riparius/ dilutes)* | | Chronic | NOEC: 4.93 (porewater) | 0.057* | 0.01 | Not exceeded |
| Fish | *Oncorhynchus mykiss* | Acute | LC$_{50}$/10: 0.093 | 0.24 | 3.0 | Exceeded |
| | *Pimephales promelas* | Chronic | NOEC: 0.15 | 0.24 | 1.9 | Exceeded |
| Amphibians (fish end-points) | | Acute, | LC$_{50}$/10: 0.093 | 1.26 | 13.5 | Exceeded |
| | | Chronic | NOEC: 0.15 | 1.26 | 8.4 | Exceeded |
| Algae (*Anabaena flosaquae*) | | Acute | EC$_{50}$/2: 0.0325 | 0.24 | 7.4 | Exceeded |
| Vascular plants (monocot, *Lemna gibba*) | | Dissolved | EC$_{50}$/2: 1.15 | 0.24 | 0.2 | Not exceeded |
| **Marine species** | | | | | | |
| Crustacean (*Americamysis bahia*) | | Acute | LC$_{50}$/2: 0.215 | 0.24 | 1.1 | Exceeded |
| | | Chronic | NOEC: 0.049 | 0.24 | 4.9 | Exceeded |
| Mollusk (*Crassostrea virginica*) | | Acute | EC$_{50}$/2: 1 | 0.24 | 0.2 | Not exceeded |
| Fish (*Cyprinodon variegatus)* | | Acute | LC$_{50}$/10: > 0.22 | 0.24 | <1.1 | Exceeded |
| | | Early-life stage | NOEC: 0.64 | 0.24 | 0.4 | Not exceeded |
| Algae (*Skeletonema costatum*) | | Acute | EC$_{50}$/2: 0.25 | 0.24 | 0.96 | Not exceeded |
| Sediment Invertebrate (*Leptocheirus plumulosus*) | | Chronic | NOEC: 1.56 (porewater) | 0.057* | 0.04 | Not Exceeded |
| * peak EEC in sediment pore water from aquatic ecoscenario modelling | | | | | | |

## Table 18 Screening Level Risk Assessment of Mandestrobin Isomers and Transformation Products for Terrestrial and Aquatic Organisms

| Organism ( exposure) | Compounds | Endpoint Value (mg/L) | EEC (mg/L) | RQ | Level of Concern |
|---|---|---|---|---|---|
| Earthworms *Eisenia foetida* (acute) | 2-COOH-S-2200 | LC$_{50}$/2:>500* | 0.92* | < 0.1 | Not exceeded |
| | 5-COOH-S-2200 | LC$_{50}$/2:>500* | 0.92* | < 0.1 | Not exceeded |
| Invertebrates *Daphnia magna* (acute) | S-2200 *R*-isomer | LC$_{50}$/2: 0.46 | 0.24 | 0.5 | Not exceeded |
| | S-2200 *S*-isomer | LC$_{50}$/2:> 7 | 0.24 | <0.1 | Not exceeded |
| | 2-COOH-S-2200 | LC$_{50}$/2: >50 | 0.26 | <0.1 | Not exceeded |
| | 5-COOH-S-2200 | LC$_{50}$/2: >50 | 0.26 | <0.1 | Not exceeded |
| | S-2200-OR | LC$_{50}$/2: >7 | 0.24 | <0.1 | Not exceeded |
| | S-2200-ORC | LC$_{50}$/2: >1.25 | 0.20 | <0.2 | Not exceeded |
| Fish *Oncorhynchus mykiss* (acute) | S-2200 *R*-isomer | LC$_{50}$/10: 0.084 | 0.24 | 2.9 | Exceeded |
| | S-2200 *S*-isomer | LC$_{50}$/10: > 1.2 | 0.24 | <0.2 | Not exceeded |
| | 2-COOH-S-2200 | LC$_{50}$/10: > 8.9 | 0.26 | <0.1 | Not exceeded |
| | 5-COOH-S-2200 | LC$_{50}$/10: > 10 | 0.26 | <0.1 | Not exceeded |
| | S-2200-OR | LC$_{50}$/10: > 0.9 | 0.24 | <0.1 | Not exceeded |
| | S-2200-ORC | LC$_{50}$/10: > 0.14 | 0.20 | <1.4 | Exceeded |

| Organism ( exposure) | Compounds | Endpoint Value (mg/L) | EEC (mg/L) | RQ | Level of Concern |
|---|---|---|---|---|---|
| Algae<br>*Pseudokirchneriella subcapitata* (acute) | S-2200 *R*-isomer | $EC_{50}$/2: 0.19 | 0.24 | 1.3 | Exceeded |
| | S-2200 *S*-isomer | $EC_{50}$/2: >6 | 0.24 | <0.1 | Not exceeded |
| | 2-COOH-S-2200 | $EC_{50}$/2: 29 | 0.26 | 0.1 | Not exceeded |
| | 5-COOH-S-2200 | $EC_{50}$/2: >27 | 0.26 | <0.1 | Not exceeded |
| | S-2200-OR | $EC_{50}$/2: >4.95 | 0.24 | <0.1 | Not exceeded |
| | S-2200-ORC | $EC_{50}$/2: >2.5 | 0.20 | <0.1 | Not exceeded |
| *mg/kg dw soil | | | | | |

**Table 19 Refined Risk Assessment of Potential Risk from Drift of Mandestrobin, S-2200 R-isomer and the Transformation Product S-2200-ORC to Aquatic Organisms**

| Organism | Exposure | Endpoint value | Refined EEC | RQ | Level of Concern |
|---|---|---|---|---|---|
| **Mandestrobin** | | | | | |
| Fish<br>*Oncorhynchus mykiss* | Acute | $LC_{50}$/10: 0.093 mg a.i./L | Aerial appl. (17% drift): 0.0401 mg a.i./L | 0.4 | Not exceeded |
| Fish<br>*Pimephales promelas* | Chronic | NOEC: 0.15 mg a.i./L | Aerial appl. (17% drift): 0.0401 mg a.i./L | 0.3 | Not exceeded |
| Amphibians<br>(fish end-points) | Acute, | $LC_{50}$/10: 0.093 mg a.i./L | Aerial appl. (17% drift): 0.214 mg a.i./L | 2.3 | Exceeded |
| | | | Ground appl. (3% drift): 0.038 mg a.i./L | 0.4 | Not exceeded |
| | Chronic | NOEC: 0.15 mg a.i./L | Aerial appl. (17% drift): 0.214 mg a.i./L | 1.4 | Exceeded |
| | | | Ground appl. (3% drift): 0.038 mg a.i./L | 0.3 | Not exceeded |
| Algae<br>*Anabaena flos-aquae* | Acute | $EC_{50}$/2: 0.0325 mg a.i./L | Aerial appl. (17% drift): 0.0401 mg a.i./L | 1.2 | Exceeded |
| | | | Ground appl. (3% drift): 0.007 mg a.i./L | 0.2 | Not exceeded |
| Crustacean<br>Mysid shrimp<br>*Americamysis bahia* | Acute | $LC_{50}$/2: 0.215 mg a.i./L | Aerial appl. (17% drift): 0.0401 mg a.i./L | 0.2 | Not exceeded |
| | Chronic | NOEC: 0.049 mg a.i./L | Aerial appl. (17% drift): 0.0401 mg a.i./L | 0.8 | Not exceeded |
| Fish<br>*Pimephales promelas* | Acute | $LC_{50}$/10: > 0.133 mg a.i./L | Aerial appl. (17% drift): 0.0401 mg a.i./L | <0.3 | Not exceeded |
| **S-2200 *R*-isomer** | | | | | |
| Fish<br>*Oncorhynchus mykiss* | acute | $LC_{50}$/10: 0.084 mg/L | Aerial appl. (17% drift): 0.0401 mg/L | 0.5 | Not exceeded |
| Algae<br>*Pseudokirchneriella subcapitata* | Acute | $EC_{50}$/2: 0.19 mg/L | Aerial appl. (17% drift): 0.0401 mg/L | 0.2 | Not exceeded |
| **S-2200-ORC** | | | | | |
| Fish<br>*Oncorhynchus mykiss* | Acute | $LC_{50}$/10: > 0.14 mg/L | Aerial appl. (17% drift): 0.034 mg/L | <0.2 | Not exceeded |

## Table 20 Risk Quotients for Aquatic Organisms Determined for Runoff of Mandestrobin, S-2200-*R*-Isomer and S-2200-ORC in Water Bodies

| Organism | Exposure | Endpoint value (mg/L) | Refined EEC (mg/L) | RQ | Level of Concern |
|---|---|---|---|---|---|
| **Mandestrobin** | | | | | |
| *Oncorhynchus mykiss* | Acute | $LC_{50}/10$: 0.093 | 0.0821 | 0.9 | Not exceeded |
| *Pimephales promelas* | Chronic | NOEC: 0.15 | 0.0821 | 0.5 | Not exceeded |
| Amphibians | Acute | $LC_{50}/10$: 0.093 | 0.223 | 2.4 | Exceeded |
| | Chronic | NOEC: 0.15 | 0.223 | 1.5 | Exceeded |
| *Anabaena flosaquae* | Acute | $EC_{50}/2$: 0.0325 | 0.0821 | 2.5 | Exceeded |
| *Americamysis bahia* | Acute | $LC_{50}/2$: 0.215 | 0.0821 | 0.4 | Not exceeded |
| | Chronic | NOEC: 0.049 | 0.0821 | 1.7 | Exceeded |
| *Cyprinodon variegatus* | Acute | $LC_{50}/10$: > 0.22 | 0.0821 | <0.4 | Not exceeded |
| ***S-2200 R*-isomer** | | | | | |
| *Oncorhynchus mykiss* | Acute | $LC_{50}/10$: 0.084 | 0.0821 | 0.98 | Not exceeded |
| *Pseudokirchneriella subcapitata* | Acute | $EC_{50}/2$: 0.19 | 0.0821 | 0.4 | Not exceeded |
| **S-2200-ORC** | | | | | |
| *Oncorhynchus mykiss* | Acute | $LC_{50}/10$: > 0.14 | 0.0821 | <0.6 | Not exceeded |

## Table 21 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

| TSMP Track 1 Criteria | TSMP Track 1 Criterion value | | Mandestrobin Endpoints |
|---|---|---|---|
| Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act*[1] | Yes | | Yes |
| Predominantly anthropogenic[2] | Yes | | Yes |
| Persistence[3]: | Soil | Half-life ≥ 182 days | Laboratory studies: $DT_{50}$ of 37.5 to 22,305 days in aerobic soil and 5 to 35 years in anaerobic soil<br>Field studies: $DT_{50}$ of 114 - 173 days |
| | Water | Half-life ≥ 182 days | $DT_{50}$ of 161 to 781 days in aquatic aerobic system and 458 days to 24 years in anaerobic aquatic systems. |
| | Sediment | Half-life ≥ 365 days | Total system $DT_{50}$ values range from 161 to 8822 days in aerobic and anaerobic water-sediment systems. |
| | Air | Half-life ≥ 2 days or evidence of long range transport | Volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure ($3.36 \times 10^{-8}$ Pa at 20°C) and Henry's law constant ($6.5 \times 10^{-12}$ atm $m^3$/mol at 20°C). |

| | | |
|---|---|---|
| Bioaccumulation[4] | Log $K_{OW} \geq 5$ | 3.51 at 25°C; Criteria not met |
| | bioconcentration factor $\geq 5000$ | 25-26 |
| | bioaccumulation factor $\geq 5000$ | Not available |
| Is the chemical a TSMP Track 1 substance (all four criteria must be met)? | | No, does not meet TSMP Track 1 criteria. |

[1] All pesticides will be considered toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the toxicity criteria may be refined if required (in other words, all other TSMP criteria are met).

[2] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

[4] Field data (for example, bioaccumulation factors) are preferred over laboratory data (for example, bioconcentration factors) which, in turn, are preferred over chemical properties (for example, log $K_{OW}$).

## Table 22 Fungicide Resistance Action Committee modes of action groups of currently registered alternative products (as of June 2015)

| Crop | Disease | Fungicide Resistance Action Committee Mode of Action groups of registered alternatives |
|---|---|---|
| **Foliar applied products** | | |
| Canola and crop subgroup 20A | White mold/sclerotinia rot | 2; 3; 7; 7+11; 9+12; 11; 44; NC* (*Coniothyrium minitans* strain CON/M/91-08) |
| Grape and crop subgroup 13-07F | Botrytis bunch rot / gray mold | 2; 7; 7+11; 7+9; 9; 9+12; 17; 44; P5; NC* (*Aureobasidium pullulans* DSM 14940 and DSM 14941; BLAD polypeptide) |
| | Powdery mildew | 3; 7; 7+9; 7+11; 11; 13; 29+M2; 44; 46; M2; M4; P5; U8; NC* (mineral oil; potassium bicarbonate; *Streptomyces lydicus* strain WYEC 108; Garlic powder; BLAD polypeptide) |
| Strawberry and crop subgroup 13-07G | Botrytis gray mold | 1; 2; 7; 7+11; 9; 9+12; 17; 44 M2; M3; M5; P5; NC* (*Trichoderma harzianum* Rifai strain KRL-AG2; BLAD polypeptide; *Streptomyces lydicus* strain WYEC 108) |
| Turfgrass | Dollar Spot | 1; 2; 3; 3+11; 3+ M5; 7; 11; 44; M5; NC* (mineral oil; *Trichoderma harzianum* Rifai strain KRL-AG2; *T. harzianum* Rifai strain T-22) |
| | Brown Patch | 1; 23; 3+11; 3+M; 7; 11; 12; 14; 44; M5 ; NC* (mineral oil; hydrogen peroxide) |
| | Fairy Ring | 3+11; 7+11; 11 |
| | Rust | 11 |
| | Take-all Patch | 3; 11 |
| Seed treatment products | | |
| Corn | *Rhizoctonia solani* seed rot | 3; 3+4+7; 7; 7+11; 11 |
| | *Fusarium* seed rot | 3; 3+4; 3+4+7; 4+11; 7; 7+11; 11 |
| Legume vegetables and crop group 6 | Rhizoctonia solani seed rot | 1+4+12; 3+4+7; 4+11; 4+11+12; 4+12; 7; 7+11; 7+M3;11; 44 |
| | *Fusarium* seed rot | 1+4+12; 3; 3+4; 3+4+7; 4+11; 4+11+12; 4+12; 7; 7+11; 7+M3; 11; 44 |
| | *Phomopsis* seed rot | 3; 3+4+7; 3+7; 4+12; 4+11; 4+11+12; 7+11; 7+M3; 11 |
| Canola and crop subgroup 20A | *Rhizoctonia solani* seed rot | 3; 3+4+12; 3+4+7+12; 3+7; 4+7+11; 7; 7+11; 7+M3; 11 |
| | *Fusarium* seed rot | 3; 3+4; 3+7; 3+4+12; 3+4+7+12; 4+7+11; 7; 7+11; 11;44 |

*NC: not classified

## Table 23 List of Supported Uses

### S-2200 4 SC Fungicide; S-2200 4 SC AG Fungicide; S-2200 4 VPP Fungicide(foliar-applied products)

| Supported claim | Conclusion and comment from value assessment |
|---|---|
| Control of white mold/sclerotinia rot (*Sclerotinia sclerottorum*) on canola (crop subgroup 20A) with one foliar application of 439 – 877 mL/ha applied when the crop is at 20-50% bloom. | Supported as proposd |
| Control of botrytis bunch rot / gray mold (*Botrytis cinerea*) on grape (crop subgroup 13-07F) with three to four foliar applications of 439 - 877 mL/ha (seasonal max. 2631 mL/ha) prior to infection during early bloom, bunch pre-closure and veraison up to 10 days before harvest with an interval of 10 days for sequential applications. | Supported as proposd |
| Suppression of powdery mildew (*Uncinula necator*) on grape (crop subgroup 13-07F) with three to four foliar applications of 439 - 877 mL/ha (seasonal max. 2631 mL/ha) prior to infection at bud break with 10 to 14 intervals. | Supported as proposd; claim limited to susceptible crops oly (grape and Amur grape) |
| Control of botrytis gray mold (*Botrytis cinerea*) on strawberry (crop subgroup 13-07G) with four to five foliar applications of 439 – 877 mL/ha (seasonal max. 3508 mL/ha) starting at 10% bloom, or prior to infection up to 0 days before harvest with reapplication intervals of 7 to 14 day. | Supported as proposd |
| Control of dollar spot (*Sclerotinia homoeocarpa*) on turfgrass with applications of 540-986 mL/ha (seasonal max. 3944 mL/ha) with 14 to 28 day intervals starting when conditions favor disease development. | Supported as proposd |
| Control of brown Patch (*Rhizoctonia solani*) on turfgrass with applications of 986 mL/ha (seasonal max. 3944 mL/ha) with 14 day intervals starting when conditions favor disease development or when the disease first appears. | Supported as proposd |
| Control of fairy ring (various basidiomycetes) on turfgrass with applications of 986 mL/ha (seasonal max. 3944 mL/ha) with 14 day intervals starting when conditions favor disease development or when the disease first appears. | Supported with the claim specified to *Agaricus campestris*rather than "various basidiomyctes" as the causal pathogen |
| Suppression of rust diseases (*Puccinia* spp.) on turfgrass with applications of 986 mL/ha (seasonal max. 3944 mL/ha) with 14 day intervals starting when conditions favor disease development or when the disease first appears. | Supported with the claim specified to 'Rust (*Puccinia graminis*)' rather than the general claim against 'Rust diseases *Puccinia* spp.' |
| Control of take-all patch (*Gaeumannomyces graminis*) on turfgrass with applications of 986 mL/ha (seasonal max. 3944 mL/ha) with 14 day intervals starting when conditions favor disease development or when the disease first appears. | Supported as proposd |

### S-2200 3.2 FS Fungicide (seed treatment product)

| Supported claim | Conclusion and comment from value assessment |
|---|---|
| Control of seed decay caused by *Rhizoctonia solani* in on corn (field corn, sweet corn, and popcorn) with one application seed of 15.6 mL/ 100 kg seed. | Supported as proposd |
| Control of seed decay caused by *Fusarium* spp. in on corn (field corn, sweet corn, and popcorn) with one application seed of 15.6 mL/ 100 kg seed. | Supported as proposd |
| Control of seed decay caused by *Rhizoctonia solani* in legume vegetables (crop group 6) with one seed application of 26 mL/ 100 kg seed. | Supported as proposd |

| | |
|---|---|
| Control of seed decay caused by *Fusarium* spp. in legume vegetables (crop group 6) with one seed application of 26 mL/ 100 kg seed. | Supported as proposed |
| Suppression of seed decay caused by *Phomopsis* spp. in legume vegetables (crop group 6) with one seed application of 26 mL/ 100 kg seed. | The causal pathogen for the claim is specified to *Phomopsis longicolla*. |
| Control of seed decay caused by *Rhizoctonia solani* in canola (crop subgroup 20A) with one seed application of 26 mL/100 kg seed. | Supported as proposed |
| Control of seed decay caused by *Fusarium* spp. in canola (crop subgroup 20A) with one seed application of 26 mL/100 kg seed. | Supported as proposed |

## Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

Mandestrobin is a new active ingredient which is concurrently being registered in Canada and the United States. The MRLs proposed for mandestrobin in Canada are the same as corresponding tolerances to be promulgated in the United States.

Once established, the American tolerances for mandestrobin will be listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide.

Currently, there are no Codex MRLs[9] listed for mandestrobin in or on any commodity on the Codex Alimentarius Pesticide Residues in Food website.

[Table 1 compares the MRLs proposed for mandestrobin in Canada with corresponding American tolerances and Codex MRLs[10]. American tolerances are listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide. A listing of established Codex MRLs is available on the Codex Alimentarius Pesticide Residues in Food website, by pesticide or commodity].

**Table 1 Comparison of Canadian MRLs, American Tolerances and Codex MRLs**

| Food Commodity | Canadian MRL (ppm) | American Tolerance (ppm) | Codex MRL (ppm) |
|---|---|---|---|
| Raisins | 7.0 | 7.0 | Not established |
| Small fruit vine climbing (Crop Subgroup 13-07F, except fuzzy kiwifruit) | 5.0 | 5.0 | Not established |
| Low growing berry (Crop Subgroup 13-07G, except cranberry) | 3.0 | 3.0 | Not established |
| Rapeseed (Crop Subgroup 20A) | 0.5 | 0.5 | Not established |
| Legume vegetables (Crop Group 6, except cowpea and field peas), corn (field, popcorn, sweet) | 0.02 | 0.02 | Not established |

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

---

[9] The Codex Alimentarius Commission is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

[10] The Codex Alimentarius Commission is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

## References

### A. List of Studies/Information Submitted by Registrant

#### 1.0 Chemistry

| PMRA Document Number | Reference |
|---|---|
| 2377784 | 2012, S-2200 Technical: Product Identity and Composition, Description of Materials Used to Produce the Product, Description of Production Process and Discussion of Formation of Impurities, DACO: 2.11.1, 2.11.2, 2.11.3, 2.11.4 |
| 2377785 | 2012, S-2200 Technical: Product Identity and Composition, Description of Materials Used to Produce the Product, Description of Production Process and Discussion of Formation of Impurities, DACO: 2.11.1, 2.11.2, 2.11.3, 2.11.4 CBI |
| 2377786 | 2013, S-2200 Fungicide Technical: Product Identity and Composition; Certified Limits; Enforcement Analytical Method, DACO: 2.12.1, 2.13.1, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9 |
| 2377787 | 2013, S-2200 Fungicide Technical: Product Identity and Composition; Certified Limits; Enforcement Analytical Method, DACO: 2.12.1, 2.13.1, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9 CBI |
| 2377788 | 2012, Preliminary Analysis and Enforcement Analytical Method of S-2200 Technical Grade for Confirmation of Its Racemic Composition, DACO: 2.13.1 |
| 2377789 | 2012, Preliminary Analysis and Enforcement Analytical Method of S-2200 Technical Grade for Confirmation of Its Racemic Composition, DACO: 2.13.1 CBI |
| 2377790 | 2012, Enforcement Analytical Methods of S-2200 Technical Grade, DACO: 2.13.1 |
| 2377791 | 2012, Enforcement Analytical Methods of S-2200 Technical Grade, DACO: 2.13.1 CBI |
| 2377792 | 2013, Analytical Method for the Determination of the Contents of S-2200 on Dry and Wet Weight Basis, DACO: 2.13.1 |
| 2377793 | 2012, Preliminary Analysis of S-2200 Technical Grade, DACO: 2.13.1, 2.13.2, 2.13.3 |
| 2377794 | 2012, Preliminary Analysis of S-2200 Technical Grade, DACO: 2.13.1, 2.13.2, 2.13.3 CBI |
| 2377795 | 2012, S-2200TG: Determination of Physical State, Colour and Odour and Relative Density, DACO: 2.14.1, 2.14.2, 2.14.3, 2.14.6 |

| | |
|---|---|
| 2377796 | 2010, Product Chemistry Testing for S-2200 PAI, DACO: 2.14.1, 2.14.12, 2.14.2, 2.14.3, 2.14.4, 2.14.5, 2.14.6, 8.2.1 |
| 2377797 | 2010, Product Chemistry Testing for S-2167 PAI, DACO: 2.14.1, 2.14.12, 2.14.2, 2.14.3, 2.14.4, 2.14.5, 2.14.6 |
| 2377798 | 2010, Product Chemistry Testing for S-2354 PAI, DACO: 2.14.1, 2.14.12, 2.14.2, 2.14.3, 2.14.4, 2.14.5, 2.14.6, 8.2.1 |
| 2377799 | 2009, Determination of the Water Solubility of S-2200 PAI, DACO: 2.14.7, 8.2.1 |
| 2377800 | 2009, Determination of the Water Solubility of S-2167 PAI, DACO: 2.14.7, 8.2.1 |
| 2377801 | 2009, Determination of the Water Solubility of S-2354 PAI, DACO: 2.14.7, 8.2.1 |
| 2377802 | 2011, S-2200 PAI - Determination of the Solvent Solubility, DACO: 2.14.8 |
| 2377803 | 2011, S-2167 PAI - Determination of the Solvent Solubility, DACO: 2.14.8 |
| 2377804 | 2011, S-2167 PAI - Determination of the Solvent Solubility, DACO: 2.14.8 |
| 2377805 | 2013, S-2200TG: Determination of the Solvent Solubility, DACO: 2.14.8 |
| 2377807 | 2013, S-2200 Dissociation Constant Waiver Request, DACO: 2.14.10 |
| 2377808 | 2011, S-2200 PAI - Determination of Vapour Pressure, DACO: 2.14.9, 8.2.1 |
| 2377810 | 2011, S-2167 PAI - Determination of Vapour Pressure, DACO: 2.14.9, 8.2.1 |
| 2377811 | 2010, Determination of the Partition Coefficient (n-Octanol/Water) -- S-2167 PAI, DACO: 2.14.11, 8.2.1 |
| 2377812 | 2010, Determination of the Partition Coefficient (n-Octanol/Water) -- S-2200 PAI, DACO: 2.14.11, 8.2.1 |
| 2377813 | 2012, Stability of S-2200 Technical Grade to Normal and Elevated Temperatures, Metals and Metal Ions, DACO: 2.14.13 |
| 2377814 | 2013, Storage Stability and Corrosion Characteristics of S-2200 Technical Grade, DACO: 2.14.14 ,2.16 |
| 2377816 | 2010, Determination of Oxidation/Reduction Properties -- S-2200 TGAI, DACO: 2.16 |
| 2377818 | 2012, S-2200 TG: Determination of Flammability, DACO: 2.16 |
| 2377820 | 2013, S-2200 - Henrys Law Constant, DACO: 2.16 |
| 2377822 | 2010, Determination of the Impact Explodability of S-2200 TGAI, DACO: 2.16 |
| 2377824 | 2011, Determination of the Thermal Explodability of S-2200 TGAI, DACO: 2.16 |

| | |
|---|---|
| 2377826 | 2012, Analytical Determination of Active Ingredient and Impurities in S-2200 Technical Grade, DACO: 2.16 |
| 2377828 | 2012, Analytical Determination of Active Ingredient and Impurities in S-2200 Technical Grade, DACO: 2.16 CBI |
| 2377830 | 2012, Confirmation of Identification of Ingredients in S-2200 Technical Grade, DACO: 2.16 |
| 2377832 | 2012, Confirmation of Identification of Ingredients in S-2200 Technical Grade, DACO: 2.16 CBI |
| 2377834 | 2013, pH of S-2200 Fungicide Technical, DACO: 2.16 |
| 2377861 | 2010, [14C]S-2167 (S-2200 R-isomer): Hydrolytic Stability, DACO: 8.2.3.2 |
| 2377863 | 2010, [14C]S-2354 (S-2200 S-isomer): Hydrolytic Stability, DACO: 8.2.3.2 |
| 2377869 | 2010, [14C]S-2354 (S-2200 S-isomer): Photodegradation and Quantum Yield in Sterile, Aqueous Solution, DACO: 8.2.3.3.2 |
| 2377871 | 2010, [14C]S-2167 (S-2200 R-isomer): Photodegradation and Quantum Yield in Sterile, Aqueous Solution, DACO: 8.2.3.3.2 |
| 2377875 | 2013, S-2200 - Stability in Air, DACO: 8.6 |
| 2443917 | 2011, Characterization of S-2200 Technical Grade and Its Related Substances, DACO: 2.13.2 |
| 2443918 | 2011, Characterization of S-2200 Technical Grade and Its Related Substances, DACO: 2.13.2 CBI |
| 2377849 | 2013, S-2200: Independent Laboratory Validation of Valent Method RM-48S-3, Determination of S-2200, DACO: 8.2.2.1, 8.2.2.2 |
| 2377854 | 2011, Validation of an Analytical Method for the Determination of S-2200 in Surface Water for Post-Registration Control and Monitoring Purpose, DACO: 8.2.2.3 |
| 2377857 | 2013, S-2200: Independent Laboratory Validation of the Analytical Method Validation of an Analytical Method for the Determination of S-2200 in Surface Water for Post Registration Control and Monitoring Purposes, DACO: 8.2.2.3 |
| 2377924 | 2011, S-2200 and Metabolites: Storage Stability of Residues in EU Soil Stored Deep Frozen, DACO: 8.6 |
| 2377958 | 2013, Calculation of Laboratory Soil Kinetics for S-2200 and its Major Metabolites According to FOCUS (2006) Guidance, DACO: 8.6 |
| 2377851 | 2013, S-2200 4 SC Ag Fungicide: Product Identity, Composition, and Analysis, DACO: 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.4.1, 3.4.2 |
| 2377853 | 2013, S-2200 4 SC Ag Fungicide: Product Identity, Composition, and Analysis, DACO: 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.4.1, 3.4.2 CBI |

| | |
|---|---|
| 2377856 | 2013, Physical and Chemical Properties of S-2200 4 SC Fungicide, VC-1902, DACO: 3.5.1, 3.5.10, 3.5.11, 3.5.12, 3.5.13, 3.5.14, 3.5.15, 3.5.2, 3.5.3, 3.5.6, 3.5.7, 3.5.8, 3.5.9 |
| 2378123 | 2013, S-2200 3.2 FS Fungicide: Product Identity, Composition, and Analysis, DACO: 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.4.1, 3.4.2 |
| 2378124 | 2013, S-2200 3.2 FS Fungicide: Product Identity, Composition, and Analysis, DACO: 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.4.1, 3.4.2 CBI |
| 2378125 | 2013, Physical and Chemical Properties of S-2200 3.2 FS Fungicide, VC-1929, DACO: 3.5.1, 3.5.10, 3.5.11, 3.5.12, 3.5.13, 3.5.14, 3.5.15, 3.5.2, 3.5.3, 3.5.6, 3.5.7, 3.5.8, 3.5.9 |

## 2.0 Human and Animal Health

| PMRA Document Number | Reference |
|---|---|
| 2377929 | 2010, Acute Oral Toxicity Study of S-2200 TG in Rats, DACO: 4.2.1 |
| 2377931 | 2011, Acute Oral Toxicity Study of De-Xy-S-2200 in Rats, DACO: 4.2.1 |
| 2377932 | 2012, Acute Oral Toxicity Study of 2-COOH-S-2200 in Rats, DACO: 4.2.1 |
| 2377933 | 2012, Acute Oral Toxicity Study of 5-COOH-S-2200 in Rats, DACO: 4.2.1 |
| 2377935 | 2012, Acute Oral Toxicity Study of 2-CH2OH-S-2200 in Rats, DACO: 4.2.1 |
| 2377936 | 2010, Acute Dermal Toxicity Study of S-2200 TG in Rats, DACO: 4.2.2 |
| 2377937 | 2010, Acute Inhalation Toxicity Study of S-2200 TG in Rats, DACO: 4.2.3 |
| 2377939 | 2010, Primary Eye Irritation Test of S-2200 TG in Rabbits, DACO: 4.2.4 |
| 2377940 | 2010, Primary Skin Irritation Test of S-2200 TG in Rabbits, DACO: 4.2.5 |
| 2377941 | 2010, Skin Sensitization Test of S-2200 TG in Guinea Pigs (Maximization Test), DACO: 4.2.6 |
| 2377943 | 2009, S-2200: 14 Day Dietary Administration Range-Finding Study in the Mouse, DACO: 4.3.1 |
| 2377944 | 2012, Acute Oral Toxicity Study of 4-OH-S-2200 in Rats, DACO: 4.2.1 |
| 2377946 | 2011, S-2200 Technical Grade: 13 Week Oral (Dietary) Administration Toxicity Study in the Mouse, DACO: 4.3.1 |
| 2377948 | 2011, S-2200 Technical Grade: 13 Week Oral (Dietary) Administration Toxicity Study in the Rat, DACO: 4.3.1 |
| 2377951 | 2008, S-2200: 1 Week Palatability Study in the Dog, DACO: 4.3.2 |
| 2377952 | 2012, S-2200 Technical Grade: 52 Week Oral (Dietary) Administration Toxicity Study in the Dog, DACO: 4.3.2 |
| 2377954 | 2012, S-2200 Technical Grade: 13 Week Oral (Dietary) Administration Toxicity Study in the Dog, DACO: 4.3.2 |
| 2377956 | 2009, S-2200: 4 Week Dietary Study in the Dog, DACO: 4.3.3 |
| 2377957 | 2011, A 28-Day Repeated Dose Dermal Toxicity Study of S-2200 Technical Grade in Rats, DACO: 4.3.5 |
| 2377959 | 2013, Waiver Request: S-2200 Fungicide Technical Subchronic (28-Day) Rat Inhalation Study, DACO: 4.3.6 |

| | |
|---|---|
| 2377960 | 2012, S-2200 Technical Grade: 78 Week Oral (Dietary) Administration Carcinogenicity Study in the Mouse, DACO: 4.4.3 |
| 2377961 | 2012, S-2200 Technical Grade: 104 Week Oral (Dietary) Administration Combined Toxicity/Carcinogenicity Study in the Rat, DACO: 4.4.4 |
| 2377962 | 2010, Dose Range-Finding Study for Two-Generation Reproduction Study of S-2200 TG in Rats, DACO: 4.5.1 |
| 2377964 | 2012, Two-Generation Reproduction Toxicity Study of S-2200 TG in Rats, DACO: 4.5.1 |
| 2377965 | 2009, S-2200 TG: Oral (Gavage) Range-Finding Study of Prenatal Development in the Rat, DACO: 4.5.2 |
| 2377967 | 2012, S-2200 TG: Oral (Gavage) Prenatal Development Toxicity Study in the Rat, DACO: 4.5.2 |
| 2377969 | 2009, S-2200 TG: Oral (Gavage) Range-Finding Study of Prenatal Development in the Rabbit, DACO: 4.5.3 |
| 2377970 | 2012, S-2200 TG: Oral (Gavage) Prenatal Development Toxicity Study in the Rabbit, DACO: 4.5.3 |
| 2377971 | 2010, Reverse Mutation Test of S-2200 TG in Bacterial Systems, DACO: 4.5.4 |
| 2377972 | 2011, Reverse Mutation Test of De-XY-S-2200 in Bacterial Systems, DACO: 4.5.4 |
| 2377973 | 2012, Reverse Mutation Test of 2-COOH-S-2200 in Bacterial Systems, DACO: 4.5.4 |
| 2377975 | 2012, Reverse Mutation Test of 5-COOH-S-2200 in Bacterial Systems, DACO: 4.5.4 |
| 2377976 | 2012, Reverse Mutation Test of 2-CH2OH-S-2200 in Bacterial Systems, DACO: 4.5.4 |
| 2377977 | 2012, Reverse Mutation Test of 4-OH-S-2200 in Bacterial Systems, DACO: 4.5.4 |
| 2377978 | 2010, Gene Mutation Assay in Chinese Hamster V79 Cells *In vitro* (V79 / HPRT) with S-2200 TG, DACO: 4.5.5 |
| 2377980 | 2011, Gene Mutation Assay in Chinese Hamster V79 Cells *In vitro* (V79/HPRT) with 2-COOH-S- 2200, DACO: 4.5.5 |
| 2377981 | 2011, Gene Mutation Assay in Chinese Hamster V79 Cells *In vitro* (V79/HPRT) with 5-COOH-S-2200, DACO: 4.5.5 |
| 2377982 | 2010, *In vitro* Chromosomal Aberration Test on S-2200 TG in Chinese Hamster Lung Cells (CHL/IU), DACO: 4.5.6 |
| 2377983 | 2012, *In vitro* Chromosomal Aberration Test on 2-COOH-S-2200 in Chinese Hamster Lung Cells (CHL/IU), DACO: 4.5.6 |
| 2377984 | 2012, *In vitro* Chromosomal Aberration Test on 5-COOH-S-2200 in Chinese Hamster Lung Cells (CHL/IU), DACO: 4.5.6 |
| 2377985 | 2010, Micronucleus Test on S-2200 TG in CD-1 Mice, DACO: 4.5.7 |
| 2377986 | 2012, Micronucleus Assay of 2-COOH-S-2200 in Mice, DACO: 4.5.7 |
| 2377987 | 2011, Metabolism of S-2200 R-isomer (S-2167) and S-2200 S-isomer (S2354) in Rats, DACO: 4.5.9 |
| 2377989 | 2012, [14C]S-2200: Absorption, Distribution, Metabolism and Excretion Following Repeat Oral Administration to the Rat, DACO: 4.5.9 |

| | |
|---|---|
| 2377990 | 2012, [14C]S-2200: Absorption, Distribution, Metabolism and Excretion Following Single Oral Administration to the Rat, DACO: 4.5.9 |
| 2377991 | 2011, An Oral (Gavage) Dose Range-Finding Acute Neurotoxicity Study of S-2200 TG in Wistar Rats, DACO: 4.5.12 |
| 2377992 | 2011, An Oral (Gavage) Acute Neurotoxicity Study of S-2200TG in Wistar Rats, DACO: 4.5.12 |
| 2377994 | 2012, A 90-Day Oral Dietary Neurotoxicity Study of S-2200 TG in Wistar Rats, DACO: 4.5.13 |
| 2377995 | 2010, Validation for the Determination of S-2200 in Dietary Formulations Using High Performance Liquid Chromatography (HPLC), DACO: 4.8 |
| 2377997 | 2010, Validation for the Determination of S-2200 in Dietary Formulations using High Performance Liquid Chromatography (HPLC), DACO: 4.8 |
| 2378000 | 2010, Validation for the Determination of S-2200 in Canine Diet using High Performance Liquid Chromatography (HPLC), DACO: 4.8 |
| 2378001 | 2011, S-2200 TG: Analytical Validation and Stability Study of Analyte Concentration in Dietary and Gavage Formulations, DACO: 4.8 |
| 2378004 | 2011, S-2200 TG: A 28-Day Dietary Dose Range-Finding Study in Wistar Han Rats, DACO: 4.8 |
| 2378005 | 2011, S-2200 TG: A 28 Day Oral (Dietary) Immunotoxicity Study in Female Wistar Han Rats, DACO: 4.8(B) |
| 2378006 | 2012, *In vitro* Steroidogenesis Assay of S-2200 TG in H295R Cells, DACO: 4.8 |
| 2378007 | 2012, Short-Term Study for Mode of Action Analysis for Mouse Liver Findings by S-2200 TG, DACO: 4.8 |
| 2378008 | 2012, Short-Term Study for Mode of Action Analysis for Rat Liver and Thyroid Findings by S- 2200 TG; -Dose Response, Time-Course, and Reversibility-, DACO: 4.8 |
| 2378009 | 2012, The Toxicological Relevance of the Liver and Thyroid Alterations Observed in Rats Treated with S-2200 TG Based on Mode of Action, DACO: 4.8 |
| 2378010 | 2012, Evaluation of Effects of S-2200 TG and its Metabolites on Human Estrogen Receptor Alpha and Human Androgen Receptor Using *In vitro* Reporter Gene Assays, DACO: 4.8 |
| 2378011 | 2013, Assessment of Toxicological Significance: Higher Incidence of Ovarian Sex-Cord Stromal Tumour in Female Rats Treated with S-2200 TG in a 2-Year Carcinogenicity Study, DACO: 4.8 |
| 2377860 | 2013, S-2200 4 SC: Acute Oral Toxicity Up and Down Procedure in Rats, DACO: 4.6.1 |
| 2377862 | 2013, S-2200 4 SC: Acute Dermal Toxicity Study in Rats, DACO: 4.6.2 |
| 2377865 | 2013, S-2200 4 SC: Acute Inhalation Toxicity Study in Rats, DACO: 4.6.3 |
| 2377866 | 2013, S-2200 4 SC: Primary Eye Irritation Study in Rabbits, DACO: 4.6.4 |
| 2377868 | 2013, S-2200 4 SC: Primary Skin Irritation Study in Rabbits, DACO: 4.6.5 |
| 2377870 | 2013, S-2200 4 SC: Local Lymph Node Assay (LLNA) in Mice, DACO: 4.6.6 |
| 2378126 | 2012, S-2200 3.2 FS: Acute Oral Toxicity Up and Down Procedure in Rats, DACO: 4.6.1 |

| | |
|---|---|
| 2378127 | 2012, S-2200 3.2 FS: Acute Dermal Toxicity Study in Rats - Limit Test, DACO: 4.6.2 |
| 2378128 | 2012, S-2200 3.2 FS: Acute Inhalation Toxicity Study in Rats, DACO: 4.6.3 |
| 2378129 | 2012, S-2200 3.2 FS: Primary Eye Irritation Study in Rabbits, DACO: 4.6.4 |
| 2378130 | 2012, S-2200 3.2 FS: Primary Skin Irritation Study in Rabbits, DACO: 4.6.5 |
| 2378131 | 2012, S-2200 3.2 FS: Local Lymph Node Assay (LLNA) in Mice, DACO: 4.6.6 |
| 2377872 | 2013, Summary of Occupational Risk Assessments for the Use of S-2200 4 SC Fungicide on Canola, Grapes, Strawberries and Turfgrass, DACO: 5.1 |
| 2377874 | 2013, Occupational and Residential Exposure and Risk Assessments for S-2200 4 SC Fungicide on Canola (Crop Subgroup 20A), Grapes (Crop Subgroup 13-07F), Strawberries (Crop Subgroup 13-07G), and Turf, DACO: 5.1 |
| 2377876 | 2013, Use Description and Scenario (Mixer/Loader/Applicator and Postapplication) for S-2200 4 SC Fungicide, DACO: 5.2 |
| 2377878 | 2013, Pesticide Handlers Exposure Database Assessment in Support of Spray Applications of S-2200 4 SC Fungicide to Canola, Grapes, Strawberries, and Turfgrass, DACO: 5.3 |
| 2377880 | 2013, Postapplication Assessment of S-2200 4 SC Fungicide Following Treatment to Canola, Grapes, Strawberries, and Turf, DACO: 5.6 |
| 2377882 | 2013, Waiver Request: Foliar Dislodgeable and Turf Transferable Residue Study for S-2200 4 SC Ag and VPP Fungicides, DACO: 5.9(A), 5.9(B) |
| 2378132 | 2013, Summary of Occupational Risk Assessments for the Seed Treatment Use of S-2200 3.2 FS Fungicide on Canola, Corn, and Soybean, DACO: 5.1 |
| 2378133 | 2013, Occupational Exposure and Risk Assessments for S-2200 3.2 FS Fungicide Seed Treatment of Corn, Legume Vegetables (Succulent or Dried) Except Cowpea and Field Pea (Crop Group 6 except Cowpea and Field Pea), Sorghum, and Canola (Rapeseed Subgroup 20A) , DACO: 5.1 |
| 2378134 | 2013, Dust Off Study in Support of the Seed Treatment Use of S-2200 3.2 FS Fungicide, DACO: 5.14 |
| 2378135 | 2013, Use Description and Exposure Scenarios for Canola, Corn, and Soybean Seed Treatment with S-2200 3.2 FS Fungicide, DACO: 5.2 |
| 2378136 | 2013, Mixer/Loader/Applicator Passive Dosimetry Study in Support of Commercial Seed Treatment of Canola, Corn, and Soybean with S-2200 3.2 FS Fungicide, DACO: 5.4 |
| 2378137 | 2013, Mixer/Loader/Applicator Passive Dosimetry Study in Support of On-Farm Seed Treatment of Soybean with S-2200 3.2 FS Fungicide, DACO: 5.4 |
| 2378138 | 2013, Postapplication: Seed Planter Passive Dosimetry Study in Support of Planting Canola, Corn, and Soybean Treated with S-2200 3.2 FS Fungicide, DACO: 5.6 |
| 2377836 | 2012, [14C]-S-2200: Absorption, Distribution, Metabolism and Excretion Following Repeated Oral Administration to the Lactating Ruminant, DACO 6.2 |
| 2377838 | 2012, [14C]-S-2200: Absorption, Distribution, Metabolism and Excretion Following Repeated Oral Administration to the Laying Hen, DACO 6.2 |
| 2377840 | 2010, Metabolism of [14C]-S-2200 in Lettuce Plants, DACO 6.3 |

| | |
|---|---|
| 2377842 | 2010, Metabolism of [14C]-S-2200 in Wheat, DACO 6.3 |
| 2377845 | 2011, Metabolism of [14C]-S-2200 in Rapeseed Plants, DACO 6.3 |
| 2378156 | 2013, Residues in Crops Grown from Seeds Treated with RS-[Benzyl-14C] S-2200 and RS- [Phenoxy-14C]-S-2200, DACO 7.8 |
| 2378157 | 2013, Characterization of Radioactive Residues of [Benzyl-14C]S-2200 and [Phenoxy-14C]S-2200 in Corn and Soybean Samples from Study VP-37088, DACO 7.8 |
| 2377859 | 2013, S-2200: Independent Laboratory Validation of Valent Method RM-48M-1 for the Determination of S-2200 in Tissue Samples, DACO 7.2.2, 7.2.3A, 8.2.2.4 |
| 2377885 | 2013, Determination of S-2200 and De-Xy-S-2200 In Crops, DACO 7.2.1 |
| 2377887 | 2013, Radiovalidation of Residue Methods for S-2200 and its Metabolites, DACO 7.2.3B |
| 2377893 | 2011, Validation of an Analytical Method for Determination of S-2200 Metabolite, De-Xy-S-2200, in Seeds of Oilseed Rape, Barley (grain and straw) and Lettuce (head), DACO 7.2.2,7.2.3A |
| 2377894 | 2011, Validation of an Analytical Method for Determination of S-2200 Metabolites, 4-OH-S-2200 and its Conjugates, in Seeds of Oilseed Rape, Barley (grain and straw) and Lettuce (head), DACO 7.2.2,7.2.3A |
| 2377896 | 2011, Validation of an Analytical Method for Determination of S-2200 Metabolites, 2-CH2OH-S- 2200 and its Conjugates, in Seeds of Oilseed Rape, Barley (grain and straw) and Lettuce (head), DACO 7.2.2,7.2.3A |
| 2377898 | 2011, Validation of an Analytical Method for Determination of S-2200 Metabolites, 5-CH2OH-S- 2200 and its Conjugates, in Barley (grain and straw) and Lettuce (head), DACO 7.2.2,7.2.3A |
| 2377899 | 2013, Independent Laboratory Validation for the Determination of S-2200 and De-Xy-S-2200 in Grapes and Canola Seed Using LC-MS/MS, DACO 7.2.2, 7.2.3A |
| 2377889 | 2010, Adaptation and Validation of Multi-Method DFG S 19 for the Determination of Residues of S-2200 in Seeds of Oilseed Rape, DACO 7.2.2, 7.2.3A |
| 2377892 | 2010, Validation of a Method based on Multi-Method DFG S 19 for the Determination of Residues of S-2200 in High-Water and Dry Crops, DACO 7.2.2, 7.2.3A |
| 2377901 | 2011, Freezer Storage Stability Study of S-2200 (its Optical Isomers of S-2167 (R-Isomer) and S-2354 (S-Isomer) in Seeds of Oilseed Rape, DACO 7.3 |
| 2377902 | 2011, Freezer Storage Stability Study of S-2200 (its Optical Isomers of S-2167 (R-isomer) and S-2354 (S-Isomer) in/on High-Water and Dry Crops over 12 Months, DACO 7.3 |
| 2377904 | 2012, Freezer Storage Stability Study of S-2200 Metabolite, De-Xy-S2200, in Lettuce (Head), Seeds of Oilseed Rape and Barley (Grain and Straw) over 12 Months, DACO 7.3 |
| 2377906 | 2012, Freezer Storage Stability Study of S-2200 Metabolite, 4-OH-S-2200, in Lettuce (Head), Seeds of Oilseed Rape and Barley (Grain and Straw) over 12 Months, DACO 7.3 |

| | |
|---|---|
| 2377908 | 2012, Freezer Storage Stability Study of S-2200 Metabolite, 2-CH2OH-S-2200, in Lettuce (Head), Seeds of Oilseed Rape and Barley (Grain and Straw) over 12 Months, DACO 7.3 |
| 2377909 | 2012, Freezer Storage Stability Study of S-2200 Metabolite, 5-CH2OH-S-2200, in Lettuce (Head) and Barley (Grain and Straw) over 12 Months, DACO 7.3 |
| 2377911 | 2013, S-2200: Magnitude of the Residue on Strawberries Grown in Canada, DACO 7.4.1, 7.3 |
| 2377917 | 2013, S-2200: Magnitude of the Residue on Strawberries, DACO 7.4.1, 7.3 |
| 2377913 | 2013, S-2200: Magnitude of the Residue on Grapes Grown in Canada, DACO 7.4.1, 7.3 |
| 2377920 | 2013, S-2200: Magnitude of the Residue on Grapes, DACO 7.4.1, 7.3, 7.4.5 |
| 2377930 | 2013, S-2200: Magnitude of the Residue on Canola Grown in Canada, DACO 7.4.1, 7.3 |
| 2377926 | 2013, S-2200: Magnitude of the Residue on Canola Grown in the United States, DACO 7.4.1, 7.3, 7.4.5 |
| 2378153 | 2013. S-2200: Magnitude of the Residue in Corn Following Seed Treatment at an Exaggerated Rate. DACO 7.4.1, 7.3 |
| 2378152 | 2013, Magnitude of the Residue of S-2200 in Soybeans Following Seed Treatment at an Exaggerated Rate, DACO 7.4.1 |
| 2377926 | 2013, S-2200: Magnitude of the Residue on Canola Grown in the United States, DACO 7.4.1, 7.3, 7.4.5 |
| 2377920 | 2013, S-2200: Magnitude of the Residue on Grapes, DACO 7.4.1, 7.3, 7.4.5 |
| 2377934 | 2011, Confined Rotational Crop Study with [14C]-S-2200, DACO 7.4.3 |
| 2377938 | 2013, S-2200: Residues in Rotational Crops Following Application of S-2200 4 SC to Leaf Lettuce, DACO 7.4.4 |
| 2377942 | 2013, S-2200: Residues in Rotational Crops Following Application of S-2200 4 SC to Canola, DACO 7.4.4 |
| 2378081 | 2013, S-2200 Fungicide: Annex IIA Tier II Summary, Residues in or on Treated Products, Food or Feed (Nature of the Residue, Level of Residue and Consumer Risk Assessment), DACO M12.7, 6.1, 7.1 |

## 3.0 Environment

| PMRA Document Number | Reference |
|---|---|
| 2377847 | 2011, S-2200 and Metabolites: Validation of an Analytical Method for Residues in EU Soil, DACO: 8.2.2.1, 8.2.2.2 |
| 2377849 | 2013, S-2200: Independent Laboratory Validation of Valent Method RM-48S-3, Determination of S-2200 and Metabolites in Soil, DACO: 8.2.2.1, 8.2.2.2 |
| 2377852 | 2013, Analytical Method Verification for the Determination of S-2200 in Sediment, DACO: 8.2.2.2 |

| | |
|---|---|
| 2377854 | 2011, Validation of an Analytical Method for the Determination of S-2200 in Surface Water for Post-Registration Control and Monitoring Purpose, DACO: 8.2.2.3 |
| 2377855 | 2012, Analytical Method Verification for the Determination of S-2200 in Freshwater and Saltwater, DACO: 8.2.2.3 |
| 2377857 | 2013, S-2200: Independent Laboratory Validation of the Analytical Method Validation of an Analytical Method for the Determination of S-2200 in Surface Water for Post Registration Control and Monitoring Purposes, DACO: 8.2.2.3 |
| 2377861 | 2010, [$^{14}$C]S-2167 (S-2200 *R*-isomer): Hydrolytic Stability, DACO: 8.2.3.2 |
| 2377863 | 2010, [$^{14}$C]S-2354 (S-2200 *S*-isomer): Hydrolytic Stability, DACO: 8.2.3.2 |
| 2377864 | 2010, [$^{14}$C]S-2354 (S-2200 *S*-isomer): Photodegradation on a Soil Surface, DACO: 8.2.3.3.1 |
| 2377867 | 2011, [$^{14}$C]S-2167 (S-2200 *R*-isomer): Photodegradation on a Soil Surface, DACO: 8.2.3.3.1 |
| 2377869 | 2010, [$^{14}$C]S-2354 (S-2200 *S*-isomer): Photodegradation and Quantum Yield in Sterile, Aqueous Solution, DACO: 8.2.3.3.2 |
| 2377871 | 2010, [$^{14}$C]S-2167 (S-2200 R-isomer): Photodegradation and Quantum Yield in Sterile, Aqueous Solution, DACO: 8.2.3.3.2 |
| 2377873 | 2013, S-2200: Waiver for Photodegradation in Air, DACO: 8.2.3.3.3 |
| 2377877 | 2010, [$^{14}$C]2-COOH-S-2200: Aerobic Degradation in Three Soils, DACO: 8.2.3.4.2 |
| 2377879 | 2010, [$^{14}$C]5-COOH-S-2200: Aerobic Degradation in Three Soils, DACO: 8.2.3.4.2 |
| 2377881 | 2011, [$^{14}$C]S-2167 (S-2200 *R*-isomer): Aerobic Soil Metabolism and Degradation, DACO: 8.2.3.4.2 |
| 2377883 | 2011, [$^{14}$C]S-2354 (S-2200 *S*-isomer): Aerobic Soil Metabolism and Degradation, DACO: 8.2.3.4.2 |
| 2377886 | 2011, [$^{14}$C]S-2167 (S-2200 *R*-isomer): Aerobic Degradation in Two Soils, DACO: 8.2.3.4.2 |
| 2377888 | 2011, [$^{14}$C]S-2354 (S-2200 *S*-isomer): Aerobic Soil Degradation in Two Soils, DACO: 8.2.3.4.2 |
| 2377890 | 2013, S-2200: Degradation Under Aerobic Conditions in Soil, DACO: 8.2.3.4.2 |
| 2377894 | 2013, S-2200: Degradation Under Aerobic Conditions in Soil - Rate Studies, DACO: 8.2.3.4.2 |
| 2377897 | 2013, S-2200: Anaerobic Soil Metabolism Study, DACO: 8.2.3.4.4 |
| 2377900 | 2013, S-2200: Degradation Under Anaerobic Conditions in Soil - Rate Studies, DACO: 8.2.3.4.4 |
| 2377903 | 2011, [$^{14}$C]S-2167 (S-2200 *R*-Isomer): Degradation in Water-Sediment Systems under Aerobic Conditions, DACO: 8.2.3.5.4 |
| 2377905 | 2011, [$^{14}$C]S-2354 (S-2200 *S*-Isomer): Degradation in Water-Sediment Systems under Aerobic Conditions, DACO: 8.2.3.5.4 |
| 2377907 | 2013, S-2200: Degradation under Anaerobic Aquatic Conditions, DACO: 8.2.3.5.6 |

| | |
|---|---|
| 2377910 | 2010, [$^{14}$C]S-2200: Adsorption/Desorption in Five Soils, DACO: 8.2.4.2 |
| 2377912 | 2010, [$^{14}$C]2-COOH-S-2200: Adsorption/Desorption in Three Soils, DACO: 8.2.4.2 |
| 2377914 | 2010, [$^{14}$C]5-COOH-S-2200: Adsorption/Desorption in Three Soils, DACO: 8.2.4.2 |
| 2377915 | 2012, [$^{14}$C]2-COOH-S-2200: Adsorption/Desorption in Three Soils, DACO: 8.2.4.2 |
| 2377916 | 2012, [$^{14}$C]5-COOH-S-2200: Adsorption/Desorption in Three Soils, DACO: 8.2.4.2 |
| 2377918 | 2013, S-2200: Estimation of Adsorption Coefficient (Koc) of 2-CONH$_2$-S-2200, 5-CONH$_2$-S- 2200 and Di-CA-S-2200 by High Performance Liquid Chromatography, DACO: 8.2.4.2 |
| 2377919 | 2013, S-2200: Soil Adsorption/Desorption, DACO: 8.2.4.2 |
| 2377921 | 2012, Leaching of S-2200 and its Major Metabolites in Two Outdoor Lysimeters, DACO: 8.2.4.3 |
| 2377922 | 2013, Summary of Storage, Disposal, and Decontamination for S-2200 Fungicide Technical, DACO: 8.4.1 |
| 2377923 | 2011, Calculation of S-2200 Sediment Water Kinetics According to FOCUS (2006) Guidance, DACO: 8.6 |
| 2377924 | 2011, S-2200 and Metabolites: Storage Stability of Residues in EU Soil Stored Deep Frozen, DACO: 8.6 |
| 2377925 | 2013, Calculation of Laboratory Soil Kinetics for S-2200 and its Major Metabolites According to FOCUS (2006) Guidance, DACO: 8.6 |
| 2377927 | 2013, S-2200: Classification of Soils Used in Foreign Environmental Laboratory Studies and Their Representation Within North America, DACO: 8.6 |
| 2377928 | 2013, Ecological Exposure of Estimated Environmental Concentrations in Surface Water Following Application of S-2200 in the United States and Canada, DACO: 8.6 |
| 2377929 | 2010, Acute Oral Toxicity Study of S-2200 TG in Rats, DACO 4.2.1 |
| 2377950 | 2013, S-2200 4 SC Ag and VPP Fungicide: Annex IIIA Tier II Summary, Fate and Behavior in the Environment, DACO: 8.1, 8.2.1, 8.2.3.1, 8.2.4.1, 8.3.1, M12.7 |
| 2377953 | 2013, S-2200: Terrestrial Field Soil Dissipation on Bare Soil in Saskatchewan, Canada, DACO: 8.3.2.1 |
| 2377958 | 2013, S-2200: Terrestrial Field Soil Dissipation on Bare Ground in Ontario, Canada, DACO: 8.3.2.1 |
| 2377963 | 2013, S-2200: Terrestrial Field Soil Dissipation on Established Turfgrass in Ontario, Canada, DACO: 8.3.2.1 |
| 2377964 | 2012, Two-Generation Reproduction Toxicity Study of S-2200 TG in Rats, DACO: 4.5.1 |
| 2377968 | 2013, S-2200: Terrestrial Field Soil Dissipation on Bare Ground in North Dakota, DACO: 8.3.2.2 |
| 2377974 | 2013, S-2200: Terrestrial Field Soil Dissipation on Bare Soil in California, DACO: 8.3.2.3 |

| | |
|---|---|
| 2377979 | 2013, S-2200: Terrestrial Field Soil Dissipation on Established Turfgrass in California, DACO: 8.3.2.3 |
| 2377988 | 2013, S-2200: Terrestrial Field Soil Dissipation on Established Turfgrass in Mississippi, DACO: 8.3.2.3 |
| 2377993 | 2013, S-2200: Terrestrial Field Soil Dissipation on Bare Ground in Georgia, DACO: 8.3.2.3 |
| 2378014 | 2009, Acute Toxicity of S-2200 TG on Earthworms, *Eisenia fetida* Using an Artificial Soil Test, DACO: 9.2.3.1 |
| 2378015 | 2011, Acute Toxicity of 2-COOH-S-2200 on Earthworms, *Eisenia fetida* Using an Artificial Soil Test, DACO: 9.2.3.1 |
| 2378016 | 2011, Acute Toxicity of 5-COOH-S-2200 on Earthworms, *Eisenia fetida* Using an Artificial Soil Test, DACO: 9.2.3.1 |
| 2378017 | 2009, S-2200 TG: Acute Oral and Contact Toxicity to the Honeybee *Apis mellifera* L. in the Laboratory, DACO: 9.2.4.1 |
| 2378018 | 2013, S-2200 Technical Grade: 72-hour Acute Toxicity of Honey bee Larvae, *Apis mellifera* L., During an In Vitro Exposure, DACO: 9.2.4.2 |
| 2378019 | 2010, S-2200 25 SC: Toxicity to the Predatory Mite, *Typhlodromus pyri* Scheuten (Acari, Phytoseiidae) in Laboratory (Rate Response Test), DACO: 9.2.5 |
| 2378020 | 2010, S-2200 25 SC: Toxicity to the Aphid Parasitoid, *Aphidius rhopalosiphi* De Stefani Perez (Hymenoptera, Braconidae) in the Laboratory (Rate Response Test), DACO: 9.2.6 |
| 2378021 | 2013, Sublethal Toxicity of S-2200 TG to the Earthworm *Eisenia fetida* in Artificial Soil, DACO: 9.2.7 |
| 2378022 | 2010, S-2200 Technical Grade - Acute Toxicity to Water Fleas, (*Daphnia magna*), Under Static Conditions, Following OECD Guideline #202, OPPTS Draft Guideline 850.1010, The Official Journal of the European Communities L383A, Method C.2 and JMAFF 12 NohSan, No. 8147 Daphnia Acute Immobilization Test (2-7-2-1) and JMAFF 13 SeiSan No 3986, DACO: 9.3.2 |
| 2378023 | 2012, 2-COOH-S-2200: Acute Toxicity to Water Fleas, (*Daphnia magna*) Under Static Conditions, Following OECD Guideline # 202 and The Official Journal of the European Communities L 142/456 Method C.2, DACO: 9.3.2 |
| 2378024 | 2012, 5-COOH-S-2200: Acute Toxicity to Water Fleas, (*Daphnia magna*) Under Static Conditions, Following OECD Guideline # 202 and The Official Journal of the European Communities L 142/456 Method C.2, DACO: 9.3.2 |
| 2378025 | 2012, S-2200-ORC: Acute Toxicity to Water Fleas, (*Daphnia magna*) Under Static Conditions, Following OECD Guideline # 202 and The Official Journal of the European Communities L 142/456 Method C.2, DACO: 9.3.2 |
| 2378026 | 2012, S-2167 (*R*-Isomer of S-2200) - Acute Toxicity to Water Fleas, (*Daphnia magna*) Under Static Conditions, Following OECD Guideline #202 and The Official Journal of the European Communities L 142/456, Method C.2, DACO: 9.3.2 |

| | |
|---|---|
| 2379027 | 2012, S-2154 (S-Isomer of S-2200) Acute Toxicity to Water Fleas, (*Daphnia magna*) Under Static Conditions, Following OECD Guideline #202 and The Official Journal of the European Communities L 142/456, Method C.2, DACO: 9.3.2 |
| 2379028 | 2012, S-2200-OR - Acute Toxicity to Water Fleas, (*Daphnia magna*) Under Static Conditions, Following OECD Guideline #202 and The Official Journal of the European Communities L 142/456, Method C.2, DACO: 9.3.2 |
| 2379029 | 2010, S-2200 Technical Grade - Full Life Cycle Toxicity Test with Water Fleas (*Daphnia magna*) Under Static Renewal Conditions, Following OPPTS Draft Guideline 850.1300, OECD Guideline #211, The Official Journal of the European Communities L225, Method C.20 JMAFF 12 NohSan, No. 8147 *Daphnia spp.* Reproduction Toxicity Studies (2-7-2-3) and JMAFF 13 SeiSan No. 3986, DACO: 9.3.3 |
| 2379030 | 2012, S-2200: A 96-Hour Shell Deposition Test with the Eastern Oyster (*Crassostrea virginica*), DACO: 9.4.2 |
| 2379031 | 2012, S-2200: A 96-Hour Flow-Through Acute Toxicity Test with the Saltwater Mysid (*Americamysis bahia*), DACO: 9.4.2 |
| 2379032 | 2012, S-2200: A Flow-Through Life-Cycle Toxicity Test with the Saltwater Mysid (*Americamysis bahia*), DACO: 9.4.5 |
| 2379033 | 2012, S-2200 - Toxicity Test with Sediment-Dwelling Midges (*Chironomus riparius*) Under Static Conditions, Following OECD Guideline 219, DACO: 9.4.5 |
| 2379034 | 2013, S-2200: A Life Cycle Toxicity Test with the Marine Amphipod (*Leptocheirus plumulosus*) Using Spiked Sediment, DACO: 9.4.5 |
| 2379035 | 2013, S-2200: A Life Cycle Toxicity Test with the Freshwater Amphipod (*Hyalella azteca*) Using Spiked Sediment, DACO: 9.3.4 |
| 2379036 | 2013, S-2200: A Life Cycle Toxicity Test with *Chironomus dilutus* Using Spiked Sediment, DACO: 9.4.5 |
| 2379037 | 2009, S-2200 Technical Grade - Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions, Following OECD Guideline #203, EC Guideline L383A, Method C.1 and OPPTS Draft Guideline 850.1075, DACO: 9.5.2.1 |
| 2379038 | 2009, S-2167 (R-Isomer of S-2200) - Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions, Following OECD Guideline #203, EC Guideline L383A, Method C.1 and OPPTS Draft Guideline 850.1075, DACO: 9.5.2.1 |
| 2379039 | 2009, S-2154 (S-Isomer of S-2200) - Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions, Following OECD Guideline #203, EC Guideline L383A, Method C.1 and OPPTS Draft Guideline 850.1075, DACO: 9.5.2.1 |
| 2379040 | 2012, 2-COOH-S-2200: Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions, Following OECD Guideline # 203 and The Official Journal of the European Communities L 142/446 Method C.1, DACO: 9.5.2.1 |

| | |
|---|---|
| 2278041 | 2012, 5-COOH-S-2200: Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions, Following OECD Guideline # 203 and The Official Journal of the European Communities L 142/446 Method C.1, DACO: 9.5.2.1 |
| 2278042 | 2012, S-2200-OH: Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions, Following OECD Guideline # 203 and The Official Journal of the European Communities L 142/446 Method C.1, DACO: 9.5.2.1 |
| 2278043 | 2012, S-2200-ORC: Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions, Following OECD Guideline # 203 and The Official Journal of the European Communities L 142/446 Method C.1, DACO: 9.5.2.1 |
| 2278044 | 2009, S-2200 Technical Grade - Acute Toxicity to Bluegill Sunfish (*Lepomis macrochirus*) Under Static Conditions, Following OECD Guideline #203, EC Guideline L383A, Method C.1 and OPPTS Draft Guideline 850.1075, DACO: 9.5.2.2 |
| 2278045 | 2009, S-2200 Technical Grade - Acute Toxicity to Fathead Minnow (*Pimephales promelas*) Under Static Conditions, Following OECD Guideline #203, EC Guideline L383A, Method C.1 and OPPTS Draft Guideline 850.1075, DACO: 9.5.2.2 |
| 2278046 | 2012, S-2200: A 96-Hour Flow-Through Acute Toxicity Test with the Sheepshead Minnow (*Cyprinodon variegatus*), DACO: 9.5.2.4 |
| 2278047 | 2010, S-2200 Technical Grade - Early Life-Stage Toxicity Test with Fathead Minnow, *Pimephales promelas*, Following OECD Guideline #210 and OPPTS Draft Guideline 850.1400, DACO: 9.5.3.1 |
| 2278048 | 2012, S-2200: An Early Life-Stage Toxicity Test with the Sheepshead Minnow (*Cyprinodon variegatus*), DACO: 9.5.3.1 |
| 2278049 | 2010, Flow-Through Bioconcentration and Metabolism Study of [$^{14}$C]S-2200 with Bluegill Sunfish (*Lepomis macrochirus*), DACO: 9.5.6 |
| 2278050 | 2009, S-2200 TG: An Acute Oral Toxicity Study with the Northern Bobwhite, DACO: 9.6.2.1 |
| 2278051 | 2011, S-2200: An Acute Oral Toxicity Study with the Canary (*Serinus canaria*), DACO: 9.6.2.3 |
| 2278052 | 2009, S-2200 TG: A Dietary LC$_{50}$ Study With the Northern Bobwhite, DACO: 9.6.2.4 |
| 2278053 | 2009, S-2200 TG: A Dietary LC$_{50}$ Study With the Mallard, DACO: 9.6.2.5 |
| 2278054 | 2010, S-2200: A Pilot Reproduction Study with the Northern Bobwhite, DACO: 9.6.3.1 |
| 2278055 | 2011, S-2200: A Reproduction Study with the Northern Bobwhite, DACO: 9.6.3.1 |
| 2278056 | 2010, S-2200: A Pilot Reproduction Study with the Mallard, DACO: 9.6.3.2 |
| 2278057 | 2011, S-2200: A Reproduction Study with the Mallard, DACO: 9.6.3.2 |
| 2278059 | 2012, S-2200-ORC: 72-Hour Toxicity Test with the Freshwater Green Alga, *Pseudokirchneriella subcapitata*, DACO: 9.8.2 |

| | |
|---|---|
| 2378060 | 2010, S-2200 Technical Grade - 96-Hour Toxicity Test with the Freshwater Green Alga, *Pseudokirchneriella subcapitata*, Following OPPTS Draft Guideline 850.5400, DACO: 9.8.2 |
| 2378061 | 2012, 2-COOH-S-2200: 72-Hour Toxicity Test with the Freshwater Green Alga, *Pseudokirchneriella subcapitata*, Following The Official Journal of the European Communities L383A, Method C.3, JMAFF 12 Nohsan, No. 8147 Alga, Growth Inhibition Test 2-7-7 and JMAFF 13 Seisan No. 3986, DACO: 9.8.2 |
| 2378062 | 2012, 5-COOH-S-2200: 72-Hour Toxicity Test with the Freshwater Green Alga, *Pseudokirchneriella subcapitata*, Following The Official Journal of the European Communities L383A, Method C.3, JMAFF 12 Nohsan, No. 8147 Alga, Growth Inhibition Test 2-7-7 and JMAFF 13 Seisan No. 3986, DACO: 9.8.2 |
| 2378063 | 2012, S-2200-OR: 72-Hour Toxicity Test with the Freshwater Green Alga, *Pseudokirchneriella subcapitata*, Following The Official Journal of the European Communities L383A, Method C.3, JMAFF 12 Nohsan, No. 8147 Alga, Growth Inhibition Test 2-7-7 and JMAFF 13 Seisan No. 3986, DACO: 9.8.2 |
| 2378065 | 2012, S-2200: A 96-Hour Toxicity Test with the Freshwater Alga (*Anabaena flos-aquae*), DACO: 9.8.2 |
| 2378066 | 2012, S-2200: A 96-Hour Toxicity Test with the Freshwater Diatom (*Navicula pelliculosa*), DACO: 9.8.2 |
| 2378067 | 2013, S-2167 (R-Isomer of S-2200) - 72-Hour Toxicity Test with the Freshwater Green Alga, *Pseudokirchneriella subcapitata*, Following the Official Journal of the European Communities L383A, Method C.3, DACO: 9.8.2 |
| 2378068 | 2013, S-2354 (*S*-Isomer of S-2200) - 72-Hour Acute Toxicity Test with Freshwater Green Alga, *Pseudokirchneriella subcapitata*, Following the Official Journal of the European Communities L383A, Method C.3, DACO: 9.8.2 |
| 2378069 | 2012, S-2200: A 96-Hour Toxicity Test with the Marine Diatom (*Skeletonema costatum*), DACO: 9.8.3 |
| 2378070 | 2012, S-2200: A Toxicity Test to Determine the Effects of the Test Substance on Seedling Emergence of Ten Species of Plants, DACO: 9.8.4 |
| 2378071 | 2012, S-2200: A Toxicity Test to Determine the Effects of the Test Substance on Vegetative Vigor of Ten Species of Plants, DACO: 9.8.4 |
| 2378072 | 2012, S-2200: A 7-Day Static-Renewal Toxicity Test with Duckweed (*Lemna gibba* G3), DACO: 9.8.5 |
| 2378073 | 2009, Analytical Method Verification for the Determination of S-2200 TG in Avian Diet, DACO: 9.9 |
| 2378074 | 2012, Method Verification for the Determination of S-2200 on Drift Cards Used to Confirm Application During Non-Target Plant Tests, DACO: 9.9 |
| 2378075 | 2011, Effects of S-2200 TG on the Activity of the Soil Microflora, DACO: 9.9 |
| 2420267 | 2012, Analytical Method Verification for the Determination of S-2200 in Freshwater and Saltwater, DACO: 8.2.2.3 |

| | |
|---|---|
| 2420268 | 2012, Analytical Method Verification for the Determination of S-2200 in Freshwater and Saltwater, DACO: 8.2.2.3 |
| 2420269 | 2013, Analytical Method Verification for the Determination of S-2200 in Sediment , DACO: 8.2.2.2 |
| 2420270 | 2013, S-2200 Technical Grade - 72-Hour Acute Toxicity of Honey Bee Larvae, *Apis mellifera* L., during an In Vitro Exposure , DACO: 9.2.4.2 |
| 2420271 | 2013, S-2200: A Life Cycle Toxicity Test with the Freshwater Amphipod (*Hyalella azteca*) Using Spiked Sediment, DACO: 9.3.4 |
| 2420273 | 2013, S-2200: A Life Cycle Toxicity Test with the Freshwater Amphipod (*Hyalella azteca*) Using Spiked Sediment, DACO: 9.3.4 |
| 2420275 | 2013, S-2200: A Life Cycle Toxicity Test with the Freshwater Amphipod (*Hyalella azteca*) Using Spiked Sediment , DACO: 9.3.4 |
| 2420276 | 2013, S-2200: A Life Cycle Toxicity Test with the Freshwater Amphipod (*Hyalella azteca*) Using Spiked Sediment , DACO: 9.3.4 |
| 2420277 | 2013, S-2200: A Life Cycle Toxicity Test with the Freshwater Amphipod (*Hyalella azteca*) Using Spiked Sediment, DACO: 9.3.4 |
| 2420278 | 2013, S-2200: A Life Cycle Toxicity Test with the Freshwater Amphipod (*Hyalella azteca*) Using Spiked Sediment , DACO: 9.3.4 |
| 2420279 | 2012, S-2200: A 96-Hour Shell Deposition Test with the Eastern Oyster (*Crassostrea virginica*), DACO: 9.4.2 |
| 2420280 | 2012, S-2200: A 96-Hour Flow-Through Acute Toxicity Test with the Saltwater Mysid (*Americamysis bahia*), DACO: 9.4.2 |
| 2420281 | 2013, S-2200: A Life Cycle Toxicity Test with the Marine Amphipod (*Leptocheirus plumulosus*) Using Spiked Sediment, DACO: 9.4.5 |
| 2420283 | 2013, S-2200: A Life Cycle Toxicity Test with the Marine Amphipod (*Leptocheirus plumulosus*) Using Spiked Sediment, DACO: 9.4.5 |
| 2420284 | 2012, S-2200: A Flow-Through Life-Cycle Toxicity Test with the Saltwater Mysid (*Americamysis bahia*), DACO: 9.4.5 |
| 2420285 | 2013, S-2200: A Life Cycle Toxicity Test with *Chironomus dilutus* Using Spiked Sediment, DACO: 9.4.5 |
| 2420286 | 2013, S-2200: A Life Cycle Toxicity Test with *Chironomus dilutus* Using Spiked Sediment, DACO: 9.4.5 |
| 2420287 | 2012, S-2200: A 96-Hour Flow-Through Acute Toxicity Test with the Sheepshead Minnow (*Cyprinodon variegatus*), DACO: 9.5.2.4 |
| 2420288 | 2012, S-2200: An Early Life-Stage Toxicity Test with the Sheepshead Minnow (*Cyprinodon variegatus*), DACO: 9.5.3.1 |
| 2420289 | 2012, S-2200: A 96 Hour Toxicity Test with the Freshwater Alga (*Anabaena flos-aquae*), DACO: 9.8.2 |
| 2420290 | 2012, S-2200: A 96 Hour Toxicity Test with the Freshwater Diatom (*Navicula pelliculosa*), DACO: 9.8.2 |
| 2420291 | 2012, S-2200: A 96 Hour Toxicity Test with the Marine Diatom (*Skeletonema costatum*), DACO: 9.8.3 |
| 2420292 | 2012, S-2200: A Toxicity Test to Determine the Effects of the Test Substance on Seedling Emergence of Ten Species of Plants, DACO: 9.8.4 |

| | |
|---|---|
| 2420293 | 2012, S-2200: A Toxicity Test to Determine the Effects of the Test Substance on Vegetative Vigor of Ten Species of Plants, DACO: 9.8.4 |
| 2420294 | 2012, S-2200: A 7-Day Static-Renewal Toxicity Test with Duckweed (*Lemna gibba* G3), DACO: 9.8.5 |
| 2420295 | 2012, Method Verification For the Determination of S-2200 on Drift Cards Used to Confirm Application During Non-Target Plant Tests, DACO: 9.9 |

### 4.0 Value

| PMRA Document Number | Reference |
|---|---|
| 2377846 | 2013. Appendix 1 - Trial Reports for "S-2200 Fungicide: Annex IIA Tier II Summary, Efficacy Data and Information on S-2200 4 SC Fungicide, Containing Mandestrobin, for Use on Canola, Grape, Strawberry and Turfgrass". DACO 10.1, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.3, 10.3.1, 10.3.2, 10.4, 10.5, 10.5.1, 10.5.2, 10.5.3, 10.5.4 |
| 2377844 | 2013. S-2200 Fungicide: Annex IIA Tier II Summary, Efficacy Data and Information on S-2200 4 SC Fungicide, Containing Mandestrobin, for Use on Canola, Grape, Strawberry and Turfgrass. DACO 10.1, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.3, 10.3.1, 10.3.2, 10.4, 10.5, 10.5.1, 10.5.2, 10.5.3, 10.5.4, M12.7 |
| 2378119 | 2013. S-2200 Fungicide: Annex IIA Tier II Summary, Efficacy Data and Information on S-2200 3.2 FS Fungicide, a Seed Protectant Containing Mandestrobin, for Control of Seed and Seedling Diseases of Canola, Corn and Soybeans. DACO 10.1, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.2, 10.2.3.3, 10.3, 10.3.2, 10.3.3, 10.4, 10.5, 10.5.1, 10.5.2, 10.5.3, 10.5.4, M12.7 |
| 2378120 | 2013. Appendix 1: Trials Reports for "S-2200 Fungicide: Annex IIA Tier II Summary, Efficacy Data and Information on S-2200 3.2 FS Fungicide, a Seed Protectant Containing Mandestrobin, for Control of Seed and Seedling Diseases of Canola, Corn and Soybeans". DACO 10.1, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.2, 10.2.3.3, 10.3, 10.3.3, 10.4, 10.5, 10.5.1, 10.5.2, 10.5.3, 10.5.4, M12.7 |

## B. Additional Information Considered

### i) Published Information

### 1.0 Human and Animal Health

| PMRA Document Number | Reference |
|---|---|
| 2409268 | U.S. EPA. 2012b. Standard Operating Procedures for Residential Pesticide Exposure Assessment. DACO 12.5.5 |
| 2528612 | Clapp, M.J.L, Wade, J.D. and D.M. Samules. 1982. Control of Nephrocalcinosis by Manipulating the Calcium:Phosphorus Ratio in Commercial Rodent Diets, Laboratory Animals, 16:130-132. DACO: 4.8 |

| | |
|---|---|
| 2528613 | Cockell, K.A. and B. Belonje. 2004. Nephrocalcinosis Caused by Dietary Calcium:Phosphorus Imbalance in Female Rats Develops Rapidly and Is Irreversible, The Journal of Nutrition, 134:637-640. DACO: 4.8 |
| 2528614 | Frazier, K.S., Seely, J.C., Hard, G.C., Betton, G., Burnett, R., Nakatsuji, S., Nishikawa, A., Durchfeld-Meyer, B. and A. Bube. 2012. Proliferative and Nonproliferative Lesions of the Rat and Mouse Urinary System, Toxicologic Pathology, 40: 14S-86S. DACO: 4.8 |
| 2528616 | Ritskes-Hoitinga, J., Lemmens, A.G., Danse, L.H.J.C. and A.C. Beynen. 1989. Phosphorus-Induced Nephrocalcinosis and Kidney Function in Female Rats, The Journal of Nutrition, 119:1423-1431. DACO: 4.8 |
| 2528615 | Woo, D.C. and R.M. Hoar. 1972, “Apparent Hydronephrosis” as a Normal Aspect of Renal Development in Late Gestation of Rats: The Effect of Methyl Salicylate, Teratology, 6:191-196. DACO: 4.8 |